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A spotlight on the adoption of the new ISUP grade groups

Kibera J, MBChB (MUK), MMed (Anat Path) (AKU)

Histopathologists are no strangers to minutiae. A brief glance down a microscope is all these expert morphologists need to take in multiple observations. It is taken for granted that the average histopathologist keeps abreast of the changing landscape of recommended practice. These recommendations often develop insidiously in Europe or America over several years, often without the knowledge of pathologists in sub-Saharan Africa, for whom professional development is often sacrificed to the pressure of daily workload. Consequently, when unveiled, these recommendations are either embraced, resisted, or simply noted with indifference all in equal measure by the individuals forming our collective practice.

The article by Nzioka *et al*[1] on "Determination of prostate cancer ISUP grade groups on archival tissue specimen at AIC Kijabe Hospital, Kenya", published in this issue is a fitting illustration of this point.

Using the ISUP grade group system, Nzioka *et al*[1] re-classified historical prostate cancer cases at AIC Kijabe hospital. Their findings highlight the predominance of higher grade group tumours in our environment with its implications to our population. They further discussed the new ISUP grading system for prostate cancer and recommended its adoption – a recommendation worth some reflection.

The development of this new grading system began in late 2014 in Chicago (USA) but of interest to this editorial is that the 2014 meeting was designed to address unresolved issues from a consensus meeting held in 2005[2].

Between 2005 and 2014, a whole decade was absorbed in thoughtful discussion on the adequacy of current prostate cancer grading practices. These discussions led to a gradual shift in perspective away from simply reporting tumour grade accurately, towards a grading system with emphasis on reproducibility, communication and prognostic significance[2]. The length of time it took to develop this new system demonstrates how, even in the most informed of societies, a significant shift in thinking can take decades. It remains to be seen how soon this new system will be adopted by the pathologists and surgeons forming the urological community in our region.

My eye is drawn to another document also written in 2005 by Dr. Debra Graves the CEO of the Royal College of Pathologists of Australasia. In the document, she describes a series of actions to be taken by the Australian government to avert a looming pathologist shortage which threatened the high standards of healthcare enjoyed by Australians. These actions were the result of about a decade of research, meetings and discussions with government about the adequacy of the pathology workforce[3].

This document appeared the same year that the initial modified Gleason grading was proposed and was followed by multiple articles assessing national and international pathology workforce output. One such article by Robboy *et al*[4] recently predicted that American pathologists will decrease to approximately 3.7 per 100,000 over the next two decades thus compromising ability to deliver quality care.

Such studies examine the big picture and foster a culture of collective introspection, allowing us to reflect on our routine practices and their effect on the quality of patient care. Development of the new ISUP grading system for prostate cancer occurred in this environment where excitement about novel scientific advancements is tempered by a sobering look at current realities and their long-term consequences on healthcare quality. Perhaps a study assessing the number of pathologists available to report prostate cancer cases, their workload and the effect of these parameters on the quality of prostate cancer grading would be a useful continuation to the work done by Nzioka *et al*[1]. It could reveal threats to patient care which adoption of the new ISUP grading system alone may not solve. Such studies

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may even usher in our own purposeful decade of discussion towards a truly homegrown shift in perspective.

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Determination of prostate cancer ISUP grade groups on archival tissue specimen at AIC Kijabe Hospital, Kenya

Nzioka A, MBChB, MMed (Anat Path)[1], **Orago A,** PhD[2], **Were T,** PhD[3]

ABSTRACT

Objective: The aim of this study was to determine the proportion of the different prostate cancer International Society of Urological Pathology (ISUP) prognostic grade groups.
Setting: These findings were part of a bigger cross sectional study done to determine the pathological characteristics of prostate cancer on archival tissue specimen at AIC Kijabe Hospital, Kenya.
Methods: Two hundred and ten prostate cancer archived tissue blocks for eligible subjects were retrieved, sectioned using a microtome and stained using routine histological Haematoxylin and Eosin stains. These stained slides were then microscopically evaluated for morphological determination of the ISUP grade group.
Results: A total of 210 prostate cancer subjects' tissue blocks were evaluated. The proportions of the different ISUP grade groups were as follows; ISUP grade group 1(23.3%), grade group 2(16.2%), grade group 3(17.1%) grade group 4(10.5%) and grade group 5(32.9%).
Conclusion: The ISUP grade group is a simplified patient-centered grading system composed of 5 prognostic grade groups for prostate cancer. The findings of this study show that our prostate cancer patients have higher ISUP grade groups (60.5% ≥ ISUP grade group 3) compared to western population (36.9% ≥ ISUP grade group 3). This points to a likelihood that prostate cancer patients in Kenyan population have a poorer prognosis at presentation than western population patients.

Key words: Prostate cancer, ISUP grade groups, Prognosis, Kenyan population

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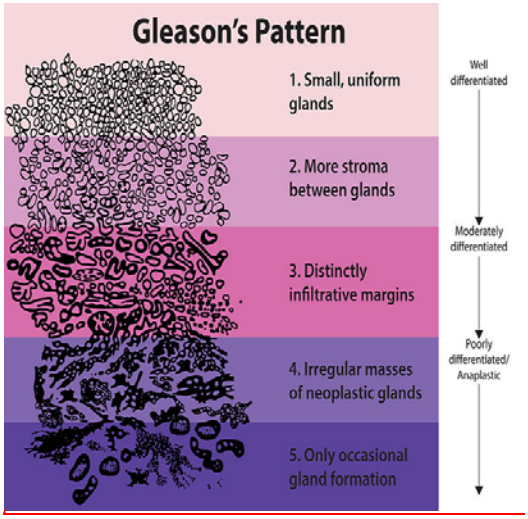
INTRODUCTION

Prostate cancer is the commonest cancer among Kenyan men according to the Nairobi cancer registry. Cancer grading is one of the prognostic parameters used in the management of PCa patients to inform treatment, follow up and outcome prediction. In clinical practice, histopathological grading of PCa is one of the most important tissue based parameter for patient prognostic stratification. The Gleason grading system is one of the best prognostic factors ever invented for PCa. Combined with other factors it is also used to stage prostate cancer. It was developed in 1966 by Donald Gleason, a pathologist at the Minneapolis Veterans Affairs Hospital[1]. Together with his team, Gleason devised grades ranging from 1 to 5, based on glandular architecture at microscopic low to medium power. These grades were shown to predict outcome in prostate cancer.

Figure 1: Gleason grading system. Artistic demonstration of the five Gleason patterns



Though the Gleason grading system has evolved over the years, it still has some challenges. Theoretically the Gleason grading system can have up to 25 different grades. Several improvements on

the Gleason grading system have been instituted. In 2005, the Gleason scoring system was altered to become the 'Modified Gleason score' by the International Society of Urological Pathology (ISUP). The criteria were refined and the attribution of certain patterns changed[2]. Gleason grades 1 and 2 were dropped since cancer with those patterns has an outcome different from grade 3. Also, pure grade 3 cancer almost never metastasizes and is reasonable to be treated by active surveillance. This has now sparked a debate about whether Gleason grade 3 should be labeled as cancer or not[3]. The International Society for Urological Pathology's (ISUP) and the WHO in 2014, adopted a simplified patient-centered grading system composed of 5 prognostic grade groups 3 as proposed in 2013 based on data from Johns Hopkins Hospital[4].The WHO/ISUP grading system consists of five grades as follows:

Table 1: WHO/ISUP grading system for prostate adenocarcinoma

Grade	Gleason score	Characteristics
Grade 1	3 + 3 =6	Histologically only composed of individual discrete well formed glands
Grade 2	3 + 4 =7	Histologically predominantly composed of well formed glands with lesser component of poorly formed/fused/cribriform glands
Grade 3	4 + 3 =7	Histologically predominantly composed of poorly formed/ fused/cribriform glands with lesser well formed glands
Grade 4	4 + 4 or 3 + 5 or 5 + 3 = 8	Histologically only composed of poorly formed/fused/cribriform glands or predominantly a mix well formed and lack of glands
Grade 5	9-10	Histologically tumour composed of no gland formation (or glands with necrosis) with or without poorly formed/fused/cribriform glands

The WHO/ISUP grading system for PCa was subsequently validated using biochemical recurrence hazard ratios on cases from 5 large academic centers[5]. The current PCa grade grouping system gives a more accurate grade stratification compared to the Gleason grading system. It has simplified grading to five grades groups with the lowest grade group being 1 as opposed to a score of 6 in the Gleason system. This will potentially reduce overtreatment of PCa. The new grading system and the terminology grade groups 1-5 were accepted and adopted by the WHO in the 2016 edition of 'Pathology and Genetics: Tumours of the urinary system and male genital organs'.

MATERIALS AND METHODS

This study was part of a PhD thesis conducted at the AIC Kijabe Hospital Pathology Department in Lari District of Kiambu County. Cochran's sample size formula for categorical data was used to get minimum sample size of 210 archived formalin-fixed, paraffin-embedded prostate cancer tissue blocks previously collected from routine simple prostatectomies. Only well-preserved archived formalin-fixed paraffin-embedded tissue blocks from PCa patients who had undergone simple prostatectomy and whose biodata was available were included into the study. Non-random purposive sampling method was used. The mean age for the patients was 74.0 years (age distribution 45.0-99.0 years).

Histopathology procedure: One histopathology section per case was cut from the retrieved formalin-fixed, paraffin-embedded tissue blocks using a microtome. Each tissue section was then stained using routine histological Haematoxylin and Eosin stains and mounted. Microscopic evaluation was done by two independent histopathologists and ISUP grade grouping done. Cases with discordant results underwent a consensus review at a multitheaded microscope with a third histopathologist.

Data analysis: Data was entered and cleaned in excel spreadsheets (MS® Office) and exported into IBM® SPSS Statistics 21.0 (SPSS Inc. Chicago, USA) for coding and statistical analyses. Data presented as tables and photomicrographs.

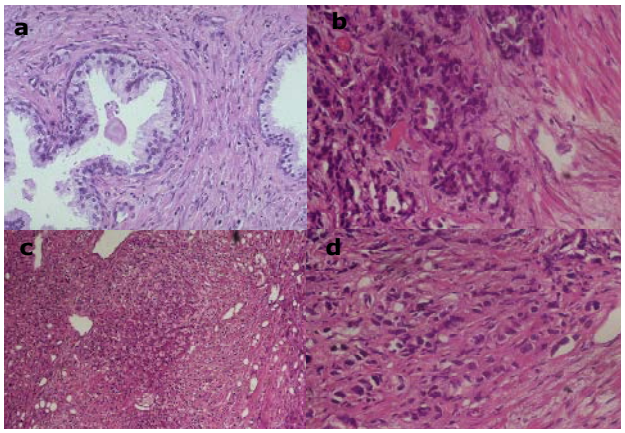
RESULTS

There was a 98% (206/210 cases) concordance between the two independent histopathologists. The discordance in the 4 cases was due to inter observer variability and was between ISUP grade group 4 and 5. A consensus grade group was arrived at by reviewing each of the four cases at a multitheaded microscope with the third histopathologist.

Table 2: Data presented as number and proportion (%) of subjects after microscopic evaluation. ISUP, (International Society of Urological Pathology)

ISUP grade groups	
Grade 1	49/210 (23.3)
Grade 2	34/210 (16.2)
Grade 3	36/210 (17.1)
Grade 4	22/210 (10.5)
Grade 5	69/210 (32.9)

Figure 2: Photomicrograph showing prostate cancer grades (x40, H&E). (a) Benign prostatic tissue, (b) PCa ISUP grade group 2, (c) PCa ISUP grade group 4, (d) PCa ISUP grade group 5



DISCUSSION

In this study, the proportions of the different ISUP grades groups were as follows; ISUP grade group 1 (23.3%), grade group 2 (16.2%), grade group 3 (17.1%) grade group 4 (10.5%) and grade group 5 (32.9%). This contrasts with findings by Samaratunga *et al*[6]. In their study, they found ISUP grade group 1 (13.5%), grade group 2 (49.6%), grade group 3 (17.6%) grade group 4 (3.7%) and grade group 5 (15.6%), respectively. Their study showed that only 36.9% of the cases were ≥ ISUP grade 3 while this study showed that 60.5% of the cases were ≥ ISUP grade 3. These findings indicate that PCa patients in this study had higher ISUP grade prostate carcinoma compared with the western population[6].

The ISUP grade groups have been accepted by the International Collaboration of Cancer Reporting (ICCR) dataset for reporting of prostate cancer which promotes structured pathology reporting in a uniform manner[7]. However, many clinicians and even pathologists are not yet conversant with the ISUP grade grouping system[7].

CONCLUSION AND RECOMMENDATIONS

The ISUP grade grouping is a simplified patient-centered grading system composed of 5 prognostic grade groups for prostate cancer. The findings of this study show that our prostate cancer patients have higher ISUP grade groups (60.5% ≥ ISUP 3) compared to western population (36.9% ≥ ISUP 3).

It is recommended that all clinicians familiarize themselves with the ISUP grade grouping system which is a simplified patient-centered grading system structured pathology reporting and hence improve patient management. To promote this familiarization, all prostate cancer diagnosis should bear both the Gleason grade and the ISUP grade group.

The ISUP grade groups give a more accurate grade stratification compared to the Gleason grading system. It has simplified grading to 5 grade groups with the lowest grade group being 1 as opposed to a score of 6 in the Gleason system. Adoption of this grading system will potentially reduce over treatment of PCa and improve patient understanding of their disease in our population.

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Conflict of interest and source of funding

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Adequacy of laboratory requisition forms submitted to cytology laboratory in Kenyatta National Hospital: a laboratory based audit study

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ABSTRACT

Background: The Laboratory Request Form (LRF) is the communication link between laboratories and users of laboratory services such as clinicians and other healthcare workers. Inadequate information or errors arising from the process of filling out laboratory request forms can significantly impact the quality of laboratory results, and patient care and safety.

Objective: The aim of this study was to evaluate the routinely submitted laboratory request forms to Cytology Laboratory in Kenyatta National Hospital for completeness.

Design: This was a cross-sectional, descriptive study.

Setting: Cytology laboratory, Kenyatta National Hospital, Kenya.

Subjects: Two hundred and twenty laboratory request forms submitted to cytology laboratory.

Methodology: Approval for this study was obtained from Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee (KNH/UON-ERC). The study approval number is UP688/11/2017. Two hundred and twenty LRFs, submitted to Cytology laboratory in the month of January, 2018, were evaluated. Analysis was done using Statistical Package of Social Sciences (SPSS) version 20.

Results: Of the 220 laboratory request forms evaluated, 79.6% were adequately completed. Only patient's name and laboratory number had 100% completion. Patient's location and clinical information/diagnosis were completed in 55.9% and 55.5% of the forms, respectively. Only 2.3% of the laboratory request forms evaluated met all the major composite quality indicator domains.

Conclusion: This study demonstrates inadequacies in performance in the filling of LRFs submitted to Cytology Laboratory, KNH. Even though some parameters were well performed, conformity to adequate filling of LRFs with all the quality indicators in the laboratory request forms was still lacking.

Recommendations: Continual medical education is required for both clinicians and other healthcare workers including laboratory staff, on the importance of adequately completing laboratory request forms.

Key words: Laboratory request forms, Cytology, Audit, Continued Medical Education

INTRODUCTION

Laboratory medicine plays a key role in helping clinicians and other healthcare workers make timely and informed decisions on patient care[1]. The laboratory analytical process is divided into pre-analytical, analytical, and post-analytical phases[2]. Studies have shown that 50% - 70% of errors which feature in the pre-analytical stage may involve handling of Laboratory Request Forms (LRFs)[3]. Laboratory request form is a communication link between a requesting physician and laboratory staff responsible for carrying out the test(s) requested. It is the mandate of a physician to complete a request form adequately before sending to the laboratory for specimen analysis. The physician ordering the test has to fill in the requisition form in a legible and accurate manner[4].

Ideally, well completed laboratory request form has to capture the information on the patient's identification details, patient's clinical information, information

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regarding the test and the requesting physician's identification details[5]. The information given should also cover the result of related biochemical and radiological investigations if applicable[6]. It is important to note that each LRF has its own peculiarity, for example, the requisition involving gynaecological or breast biopsy specimens must be accompanied, in addition to other information, by the patient's date of last regular menses and contraceptive-use profile[7].

The LRF should contain the following information; patient's and physicians' identifiers, patients' clinical and sample information. Patients' identifiers include details of the patient whose sample is to be analysed in the laboratory. These include the full names of the patient, sex, age, hospital number, request date and patient's location (ward). Patient's details on sex and age is of great importance as some cancers/diseases are age specific and/or gender specific[8]. This information directs the laboratory personnel to make proper conclusions regarding the findings. The date the request was made is important in prioritizing sample to work on first. The hospital number together with the patient's location makes it possible to access the patient in some cases like repeat sample collection. Patients' identifiers therefore link the patient to the sample, test ordered, and the results.

Physician's identifiers include the doctor's name, practise number, signature and contacts. This provides a link to the requesting physician. Any deviation or inappropriateness of a test can be communicated to a specific doctor, thus enhancing accountability which translates to a quality healthcare. It further ensures that only licenced physicians are involved in making laboratory requisitions[9].

Patient's clinical information is a medical information of the patient's clinical status captured in the specific section of the LRF. For the gynaecological request forms, this section contains; age, Last Menstrual Period (LMP), hormone therapy, birth control pill usage, cervical biopsy details, history of dysplasia, previous Papanicolaou (PAP) smear findings, hysterectomy, Intra-Uterine Devices (IUD), abnormal bleeding, history of radiation, history of any malignancy, and any other relevant clinical information[10]. These provide direction to pathologists to the right track as they observe the morphology of cells to make a diagnosis. Usage of birth control pills mimics the action of oestrogen and progesterone and increase the thickness of the cervical plug[11]. Such information will help cytopathologists to make a correct opinion and therefore reduce false negatives or positives in the observed slides.

For the non-gynaecological request forms, this section contains previous history indicating any previous tumour and previous treatment such as radiotherapy or chemotherapy. Information on previous treatment is important as it has been established that many drugs have the ability to affect the interpretation of cytological results[12,13]. The provisional diagnosis indicated on the request form, in some cases, can also have effects on the correct interpretation of the results[14]. In Fine Needle Aspiration Cytology (FNAC) the cytologist need to know the patient's clinical history, previous diagnosis and, where appropriate, clinical staging so as to arrive at a meaningful interpretation[15].

Sample information includes; the type of the sample, source, and date of collection. Time of collection is also indicated when necessary. Samples have multiple sources, hence, specificity of the sample type and source is very key in the laboratory. For instance, samples for FNAC have more than one source which calls for specificity of proper documentation of the type and source of the sample for effective interpretation of the results. Recording of the date and time of sample collection ensures that turn-around time is observed for each specimen in the laboratory. Special samples, for example, Cerebrospinal Fluid (CSF) requires a specification of time of collection since it contains enzymatic agents that will cause deterioration of cells if not processed within 1-2 hours after collection[15].

Inadequately filled request forms poses difficulties in both diagnostic processing and infection control surveillance. This is a challenge in most healthcare systems as it makes laboratory personnel to give wrong results jeopardizing the patients' care and safety in terms of the unreliability of the results, as well as subjecting them into unnecessary and undeserving treatments. This research was designed to establish the extent of completeness of laboratory request forms in a major referral hospital in Kenya, where cytology is widely practised.

MATERIALS AND METHODS

This study was conducted from 1st January, 2018 to 31st January, 2018 after obtaining approval from Kenyatta National Hospital and the University of Nairobi Ethics and Research Committee (KNH-UoN ERC). Study approval

number is UP688/11/2017. Two hundred and twenty LRFs were obtained using simple random sampling. The following parameters were captured into a password-protected computer database using Microsoft Excel version 2013: patient's name, patient's age, patient's gender, patient's location (ward), patient's history, hospital number, sample type, request date, date of sample collection, physician's identity, clinical information or diagnosis and laboratory number. These were recorded as complete when filled or not complete when not filled. Analysis was done using Statistical Package of Social Sciences (SPSS) version 20.

RESULTS

Completion of the request forms: A total of 220 LRFs, containing 12 data elements, were evaluated (Table 1). Overall, 79.6% of LRFs were filled out completely. Only patient's name and laboratory number in all the LRFs evaluated had 220(100%) completion. Indication of the hospital number in all the forms evaluated was 209 (95.0%). Patient's age had a completion percentage of 94.1% (n=207) followed closely by the patient's gender which was 206 (93.6%).

All the other remaining data elements had a completion percentage of at least 60.0%, except for request date and clinical information/ diagnosis which scored 123(55.9%) and 122 (55.5%) respectively. The completion of the patient's location was found to be 197 (89.5%), and the physician's identification; which was evaluated by name, signature or both, was found to have a completion percentage of 86.4% (n=190). The date sample requested had a completion percentage of 60.5% (n=133), and on the other hand, the sample collection date was found to be 142 (64.5%). The history of the patient in the LRFs evaluated were indicated in 132 (60.0%) of the forms.

Overall, of the LRFs evaluated, 5 (2.3%) met all the quality indicators while 97.7% failed to meet all the quality indicators (Table 2). Laboratory detail was completed in all the LRFs 220 (100%), that were evaluated. Laboratory number was the only element that was used in the assessment of the laboratory detail quality indicator. This was followed by patient identifiers which were complete in 195 (88.7%) forms while the physician details was complete in 190 (86.4%). The indication of the test request details in the LRFs evaluated was found to be complete in 130 (59.1%) forms.

Table 1: Completeness of laboratory request forms submitted to cytology laboratory at Kenyatta National Hospital

Laboratory request form elements	Completed		Not completed	
	n	(%)	n	(%)
Patient's name	220	100	0	0.0
Patient's age	207	94.1	13	5.9
Patient's gender	206	93.6	14	6.4
Patient's location	197	89.5	23	10.5
Patient's history	132	60.0	88	40.0
Hospital number	209	95.0	11	5.0
Sample type	123	55.9	97	44.1
Request date	133	60.5	87	39.5
Sample collection date	142	64.5	78	35.5
Physician's identity	190	86.4	30	13.6
Clinical information/diagnosis	122	55.5	98	44.5
Laboratory number	220	100	0	0.0
Overall percentage		79.6		20.4

Table 2: Performance on the major quality indicators according to International Federation of Clinical Chemistry

	Completed		Not completed	
Quality indicator domain	n	(%)	n	(%)
Patient identifiers	195	88.7	25	11.3
Test request details	130	59.1	90	40.9
Physician identifiers	190	86.4	30	3.6
Laboratory detail	220	100	0	0.0
All quality indicators met	5	2.3	215	97.7

DISCUSSION

Completion of the request forms: Overall, it was found out that 79.6% of the LRFs evaluated were completed and this finding is in agreement with the previous findings of a study conducted in Ile-Ife, Nigeria which showed 84% overall completion of LRFs16. It was also realized that the most adequately filled LRFs' elements were patient's name 220 (100%) and laboratory number 220 (100%). The adequacy of the patient's name indication and laboratory number is consistent with the findings of a study conducted at Aminu Kano Teaching Hospital in Kano, Nigeria where adequacy of both patient's name and laboratory number showed 100% compliance for the forms submitted to Department of Haematology, and 100% and 99.7% for the ones submitted to blood transfusion services respectively[17]. The adequacy of the patient's name indication in our findings is also consistent with the findings of a study conducted at Bharati Hospital and Research Centre, a Tertiary Care Teaching Hospital in Pune, India where it was found out that the percentage error in filling out the patients' name in the LRFs submitted in all Outpatient Departments (OPDs) was 1.96% translating to an adequacy percentage of 98.04%[18]. The Medicine OPD and the Obstetrics and Gynaecology OPD both had 94.74% completion, the ones submitted to Surgery OPD had 99.39% completion, and the forms submitted to Paediatrics and other OPDs had 100% completion of the patient's name[18]. The patient's name is the first point of identifying a sample from clinic or at any collection location. In the laboratory, alongside the name, the sample is assigned a unique number for a more definite and convenient identification.

In this study, patient's age and gender was filled in 207 (94.1%) and 206 (93.6%) of the LRFs evaluated respectively. These findings are consistent with the findings of a study done at Ile-Ife Nigeria where the completion of patient's age and gender was 86.4% and 99.8% respectively[16]. The findings from this study also demonstrates consistent findings in a study done in India, indicating a 15.9% defect in the completion of patient's gender. This translated to 84.5% completion[18]. On the other hand, our findings are in sharp contrast with the findings from a Ghanaian study where the reported completion of patient's age was 25.6% and patient's gender 32.7%[19]. Similar findings were also obtained in a study conducted in Lagos which demonstrated that 68% of the forms analysed had patient's age completely filled[5].

Our study reported that the physician information was completed in 190 (86.4%) of the forms which is lower than the 96.6% completion of the consultant-in-charge (Physician) information from a study in Ile-Ife, Nigeria[16], and in addition, a study in Bharati Hospital and Research Centre in Pune, India also reported 4.16% defects in the completion of the doctor's name and signature which translated to 95.84% completion[18]. This variation could have been due to doctors' failure to complete this important section which ensures link between the requesting doctor and the laboratory personnel in a case of critical results. However there are consistent reports from a study in South Africa which reported 86.6% completion of the physician details and contacts, as well as a Nigerian study which reported 90.1% completion of the physician name and signature[17].

It was found out, in this study, that the indication of the patient's location was completed in 197 (89.5%) of the forms evaluated, and hospital number completion was 209 (95%). The finding, in patient's location, is in conformity with the findings of a study conducted in a Nigerian Specialist Hospital which demonstrated 88.6% completion of the ward number in the LRFs evaluated[20]. On the other hand, the finding is in contrast with the report of the study at Aminu Kano Teaching Hospital in Kano, Nigeria where it was reported that the indication of patient's location was done in 100% of the forms analysed[17]. The reported hospital number completion is

consistent with the reported 2.19% completion defect, in an Indian study which translated to 97.81% completion, of the OPD number in the LRFs evaluated[17]. The consistency is also shown in a report of a study in a Nigerian Specialist Hospital where the completion of the unit number was found to be 87.1% of the LRFs evaluated[20]. Jegede *et al*[17] too reports a consistent finding with our study where it was found out that the completion of hospital number was 94.3% and 98.6% in the LRFs submitted to Blood Transfusion Services and Department of Haematology respectively.

Our study demonstrated 132 (60.0%) adequately completed patient's history, and 122 (55.5%) adequately completed clinical information/diagnosis. This report is consistent with the reported 57.8% defect in filling clinical notes, translating to 42.20% completion, in a study done in India[16]. Our report is also consistent with findings of a study conducted in a Nigerian Specialist Hospital which indicated clinical information/diagnosis in 64.9% of the forms evaluated20. On the contrary, the findings from this study is far much below the findings of a study carried out at Aminu Kano Teaching Hospital in Kano, Nigeria where it was found out that 80.9% and 99.8% of the forms, submitted to Blood Transfusion Services and Department of Haematology respectively, had completed clinical information/diagnosis for the patients[17].

This study found out that the sample type submitted to the laboratory was indicated in 122 (55.9%) of the forms evaluated. The request date was completed in 133 (60.5%) of the forms, and the sample collection date completed in 142 (64.5%) of the LRFs evaluated. The sample type completion, is in sharp contrast with the findings of a study done at Ile-Ife, Nigeria which reported 89.9% indication of the sample type in the LRFs evaluated[16]. Another study showing sharper contrast with my findings is the one done at Aminu Kano Teaching Hospital in Kano, Nigeria where it was reported that sample type was completed in 92.2% and 99.7% of the forms submitted to Blood Transfusion Services and Department of Haematology, respectively. The request date from this study is also contrasting the findings of the Nigerian study which reported 92.7% and 99.5% completion of request date in the LRFs submitted to Blood Transfusion Services and Department of Haematology respectively[16]. The findings of sample collection date in this research is as well consistent with the reported findings of 99.7% completion in a Nigerian study[20]. These findings could be due to handling of many patients by few requesting physicians at a time.

A major limitation of this study is that doctors' opinion for the inadequacies of LRFs were not sought. Opinion from other health care workers including laboratory personnel was not also sought as they were not directly involved in the filling of the request forms that were reviewed.

This study demonstrates inadequacies in performance in the filling of LRFs submitted to cytology laboratory. Even though some parameters were well performed, conformity to adequate filling of LRFs with all the quality indicators in the laboratory request forms was still lacking. Continual medical education is required for both clinicians and other healthcare workers including laboratory staff, on the importance of adequately completing laboratory request forms.

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Detection of *Helicobacter pylori* using immunohistochemistry at the Kenyatta National Hospital histopathology laboratory

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ABSTRACT

Background: *Helicobacter pylori,* is a Gram negative bacteria that colonizes the gastric mucosa and is responsible for upper gastrointestinal symptoms. Endoscopy and biopsy are carried out to assess the cause and extent of chronic gastritis. Histochemical stains have been shown to perform poorly when compared to immuno histochemistry. There is a need to improve on the detection rates to accurately establish the cause of the gastritis.
Objective: To detect *Helicobacter pylori* in gastric mucosa biopsies using immuno histochemical methods.
Methods: This was a descriptive cross-sectional study. The sample size was seventy-eight. Haematoxylin and Eosin and Giemsa staining was routinely carried out to describe the pattern of gastritis and presence of *Helicobacter pylori* infection. Samples that turned out negative underwent immunohistochemical staining to detect *Helicobacter pylori.* Data was collected based on the Updated Sydney classification of gastritis and analyzed using SPSS version 21.0. Assessment was done to correlate if there was a significant improvement in the detection rates based on the various histopathologic findings seen on routine staining.
Results: The mean age of the patients was 48.9 years with a standard deviation of 18.7. Chronic inactive gastritis was the most common Haematoxylin and Eosin finding, which was seen in 82.1% of the cases. Severe inflammation (+3) was present in half (50%) of the samples. Immunohistochemical positivity was found in 25.6% (20 of 78) of the samples. Presence of lymphoid aggregates correlated significantly with positive staining ($p = 0.032$, OR 3.1). There was no other statistically significant histopathologic finding.
Conclusion: Immunohistochemistry is a reliable technique in detection of *Helicobacter pylori,* especially when lymphoid aggregates are present. Haematoxylin and Eosin stain adequately displays the inflammatory and adaptive changes while Giemsa staining still remains the preferred technique to visualize *H. pylori.*
Recommendation: Immunohistochemistry should be introduced in the histopathology laboratory to detect *Helicobacter pylori* infection.

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INTRODUCTION

Helicobacter pylori (H. pylori) is a spiral-shaped Gram-negative rod that colonizes the gastric mucosa. It has colonized humans naturally for over 50,000 years. It is the main risk factor for antral gastritis, peptic ulcers, gastric ulcers, gastric adenocarcinoma and gastric Mucosa-Associated Lymphoid Tumour (MALT)[1]. It is mostly acquired in childhood and by the age of 10 years; more than 50% of children worldwide carry the organism. A declining prevalence in developed countries may be due to decreased transmission because of less crowding and frequent exposure to antimicrobials. It is estimated that 80% of the population in developing parts of the world are infected by the age 20 years[2]. In Kenya, a study done in 696 patients with dyspepsia revealed the prevalence among children at 73.3% and among adults at 54.8%. Infection rates were 56% in rural Kenyan Africans, 62% in urban Kenyan Africans and in urban Kenyan Asians at 58%. This was determined by endoscopic evaluation[3]. In another study, 445 stool antigen tests for children between 18 months and 15 years old were performed. *H. pylori* was positive in 99 (22%) children; with 64% of the positive tests from children aged 8 years and above. In the same period, *H. pylori* was identified in 44 out of 74 (59%) endoscopy biopsies

with the youngest patient aged 3 years. In all cases, there was equal distribution among males and females[4].

H. pylori is found deep in the mucous layer near the epithelial surface where physiological pH is present. *H. pylori* is motile and can move from the mucous layer to the epithelial surface resulting in mucosal damage and inflammation[5]. Colonization by *H. pylori* induces a specific tissue response - chronic superficial gastritis - which is accompanied by cell-mediated and humoral responses. There also is down regulation of the immune system resulting in ineffective clearance of the bacteria. Development of overt disease depends on a complex interplay between bacterial strain differences, host susceptibility to disease and environmental factors[1]. Acute infection causes marked inflammation in the antrum and body, inhibition of parietal cell function and eventually hypochlorhydria. There is increased gastrin level due to lack of normal inhibition of gastrin release exerted by gastric acid and loss of G cells with antral mucosa atrophy. Persistent infection leads to atrophy with increased risk of adenocarcinoma; which develops due to epithelial cell proliferation in a setting of chronic inflammation. Certain strains contain a pathogenicity island that has cytotoxin-associated A (cag-A) gene which penetrates epithelial cells. This initiates a signal cascade akin to unregulated growth factor stimulation.

Malignancy tends to occur against a background of a body predominant gastritis and presence of atrophy. In duodenal ulcer disease, *H. pylori* reduces bicarbonate secretion causing mucosal damage and gastric metaplasia. This enables *H. pylori* to colonize this region. There is also elevated gastrin levels[6].

Diagnostic tests are divided into invasive tests; based on gastric specimens, and non invasive tests; based on peripheral samples. Histological detection is still taken as the gold standard test for diagnosing infection[7]. For routine diagnosis, histology and culture, urea breath test and stool antigen test are used most often while serology is used mainly in epidemiological studies[5]. Upper gastrointestinal endoscopy is used to assess the effect of infection. Assessment of gastric biopsies enables the histopathologist to determine the cause of the gastritis through routine staining. In 1990, based on new aetiological facts on gastritis, a new classification system was presented at the World Congress of Gastroenterology in Sydney, Australia. It was later updated in 1994 at the *H. pylori* congress in Houston, United States. The Sydney system for the classification of gastritis emphasized the importance of combining topographical, morphological and aetiological information that would help generate reproducible and clinically useful diagnoses[8]. The report generated includes the type of gastritis - active, chronic or other, the grade of Helicobacter density, activity (neutrophilic infiltration), chronic inflammation, glandular atrophy, intestinal metaplasia, the location of gastritis – antrum, fundus/body, cardia, diffuse and other features (ungraded) such as granulomas, eosinophils, intraepithelial lymphocytes[9].

H. pylori can be identified on H&E stain but recognition is enhanced with Giemsa stain. Other histochemical stains enhance detection such as Warthin-Starry or Steiner silver stains, Genta stain and Alcian yellow-toluidine blue method. Recently, newer methods have been introduced such as immunohistochemistry (IHC) and Polymerase Chain Reaction (PCR). PCR has improved detection by 20-40% in histologically negative biopsies[7]. In a study comparing H&E, Giemsa and toluidine blue staining with IHC reviewed 54 gastric biopsy specimens, *H. pylori* was positively identified by IHC in 43 (79.63%) patients, 18 (33.33%) by H&E, 24 (44.44%) by Giemsa and 33 (61.11%) using toluidine blue staining methods[10]. The advantages of IHC are that it is less demanding than WS silver stains, reliable, easy to use and interpret and that it is able to detect low numbers of organisms and coccoid forms. The disadvantages of IHC are financial constraints that limit its use for routine purposes, it is time consuming and that negative controls need to be used with every slide.

There is a high prevalence of *Helicobacter pylori* based on epidemiologic studies carried out in Kenya. However, on histopathological examination of gastric biopsies, the detection rate is lower than prevalence. This may be due to poor sensitivity of the H&E and Giemsa stains. Accurate detection of *H. pylori* will assist clinicians provide appropriate treatment to their patients. Immunohistochemistry is a superior technique in determining the cause of chronic gastritis; especially without obvious evidence of *H. pylori*[11].

MATERIALS AND METHODS

The broad objective was to detect *Helicobacter pylori* in gastric mucosa biopsies using immunohistochemical methods at KNH histopathology laboratory. The specific objectives were to review the histomorphology of gastric

biopsies submitted to KNH histopathology laboratory and compare Giemsa-negative *H. pylori* biopsies with immunohistochemistry staining.

This was a cross-sectional study done at the Kenyatta National Hospital histopathology laboratory in conjunction with the UON immunohistochemistry section of the Department of Human Pathology. Thirty gastric biopsies were collected from the KNH Endoscopy Unit while fifty-nine samples were retrieved from archived blocks in the KNH histopathology laboratory. Ethical approval was sought from Kenyatta National Hospital/University of Nairobi Scientific and Ethical Review Committee (KNH-UON ERC). The inclusion criterion was gastric biopsies reported as *H. pylori* negative on Giemsa stain. The exclusion criteria were biopsies with severe gastric atrophy and gastric malignancy. Samples that were positive on H&E and Giemsa stains were not stained by IHC as treatment regimen for *H. pylori* would not alter depending on the method used. Simple random sampling technique using a table of random numbers was used to select the biopsies that were included in the study until the required sample size of 78 was reached.

Samples from the archive diagnosed as chronic gastritis was selected by the first author. Random sampling was done. Paraffin blocks were retrieved. Staining with H&E and Giemsa was carried out to review the histomorphologic pattern and confirm absence of *H. pylori.* Cases that met the inclusion criteria underwent IHC staining. Screening was done by the Principal Investigator and the findings confirmed with supervisors. For the samples collected from the Endoscopy Unit, a report was availed within one week directly to the clinician by the Principal Investigator for further management. For positive result for *H. pylori* the immunostain stained the bacteria brown while the background consisting of the gastric mucosa stains light purple to white based on cellular constituents. A negative result showed mucosa without any organisms visibly stained. For quality assurance purposes, Immunohistochemistry reagents were stored at 2-8°C to maintain stability. Pre-diluted reagents were used to avoid dilution errors and pre-charged slides were used. Specimen collection and staining for IHC was done according to the protocol. Controls, both negative and positive, were used at regular intervals during the staining. Any discordant results were reviewed by a third reviewer - the KNH Pathologist.

The data collection tools were coded and entered in Microsoft Access 2013 database designed for the study. Data cleaning was performed continuously during data collection and entry. At the end of data collection, cleaned data was exported to SSPS version 21.0 for statistical analysis. Study population was described using age and sex summarized into mean, standard deviation and percentages respectively. Prevalence of *H. pylori* based on immunohistochemistry results was analyzed and presented as a percentage with 95% confidence interval. Histomorphology of the specimens was presented as percentages. Percentage of adequate biopsies was calculated out of all the specimens reviewed and presented as tables, histograms and pie charts.

RESULTS

Table 1: Socio-demographic details of patients who underwent endoscopy (N=78)

Variable	Frequency (%)/ mean (SD)
Mean age (SD)	48.9 (18.7)
Gender	
Male	37 (47.4)
Female	41 (52.6)

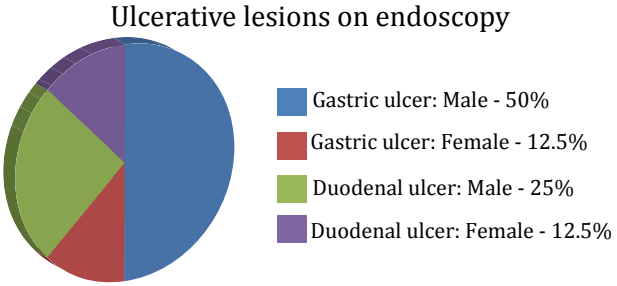
The youngest patient was 7 years old at the time of endoscopy, while the oldest was 92 years. The M:F ratio was 1:1.1.

Table 2: Endoscopy findings of patients who underwent endoscopy (N=78)

Variable	Number	Frequency (%)
Gastritis	19	(24.4)
Gastric ulcer	10	(12.8)
Duodenal ulcer	6	(7.7)
Gastric polyp	4	(5.1)
Doudenal polyp	1	(1.3)
Normal mucosa	30	(38.5)
Duodenitis	2	(2.6)
Hiatus hernia	3	(3.8)
Not provided	3	(3.8)
Total	78	100%

Gastric ulcers were present in 8 males and 2 females; with a male to female ratio of 4:1. The ratio of duodenal ulcers was 2:1, with prevalence of 4 males and 2 females (Figure 1).

Figure 1: Male to female ratio of ulcers found on endoscopy (N=78)



The most common histopathology findings on Haematoxylin and Eosin staining were chronic inactive inflammation (82.1%) and severe inflammation (50%). Atrophy, intestinal metaplasia, lymphoid aggregates, mucosal erosions, eosinophilic infiltration and numerous cocci were absent in 87.2%, 84.6%, 60.3%, 89.7%, 83.3% and 89.7% of cases respectively.

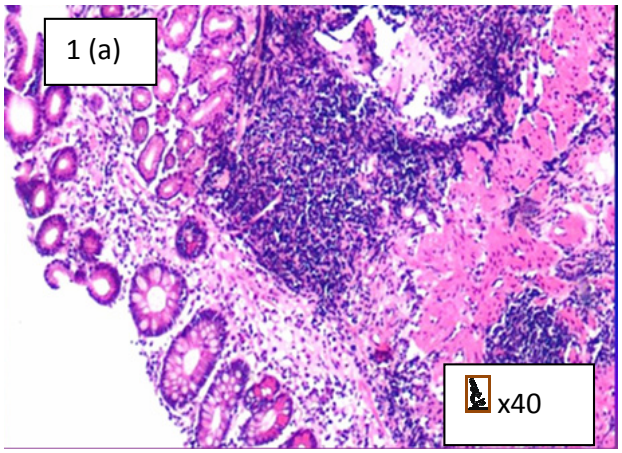
On immunohistochemistry staining, *H. pylori* was positive in 25.6% of cases. Of these, 85% showed a low degree (+1) of degree colonization. There was a medium quality of staining of the organisms and background in 17.9% and 83.3% respectively of the total cases. Of the *H. pylori* positive cases, 70% (14 of 20 cases) showed medium quality of organism morphology. The findings on endoscopy had no statistical significance with the severity of inflammation (none had p value of < 0.05).

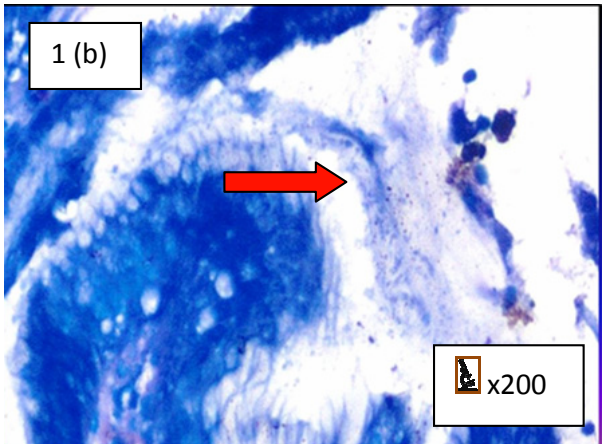
Biopsies with lymphoid aggregates were more likely to have positive staining on immunohistochemistry (38.7%) compared to 17% in those with no lymphoid aggregates, OR 3.1 (95% CI 1.1-8.8), p = 0.032. The severity of inflammation, presence of atrophy, intestinal metaplasia or ulcers had no statistical significance on immunohistochemical methods (p > 0.05).

Table 3: Correlation between microscopy or endoscopy findings and *H. pylori* staining on immunohistochemistry (N=78)

Variable	Helicobacter pylori staining		OR (95% CI)	P value
	Positive (%)	Negative (%)		(X^2 test)
Microscopy findings				
Type of inflammation				
Chronic active	3 (21.4)	11 (78.6)	0.8 (0.2-3.0)	1.000
Chronic	17 (26.6)	47 (73.4)	1.0	
Severity of inflammation				
Mild	0	6 (100.0)	-	
Moderate	9 (27.3)	24 (72.7)	1.0 (0.3-2.7)	0.999
Severe	11 (28.2	28 (71.8)	1.0	0.930
Presence of atrophy				
Yes	2 (20.0)	8 (80.0)	0.7 (0.1-3.6)	1.000
No	18 (26.5)	50 (73.5)	1.0	
Presence of intestinal metaplasia				
Yes	5 (41.7)	7 (58.3)	2.4 (0.7-8.8)	
No	15 (22.7)	51 (77.3	1.0	0.278
Presence of lymphoid aggregates				
Yes	12 (38.7)	19 (61.3)	3.1 (1.1-8.8)	0.032
No	8 (17.0)	39 (83.0)	1.0	
Atrophy/severe inflammation/ intestinal metaplasia/ lymphoid aggregates				
Yes	14 (28.6)	35 (71.4)	1.5 (0.5-4.6)	0.441
No	6 (20.7)	23 (79.3)	1.0	
Endoscopy findings				
Gastric ulcer				
Yes	3 (30.0)	7 (70.0)	1.3 (0.3-5.5)	0.711
No	17 (25.0)	51 (75.0)	1.0	
Duodenal ulcer				
Yes	2 (33.3)	4 (66.7)	1.5 (0.3-8.9)	0.643
No	18 (25.0)	54 (75.0)	1.0	

Figure 2: Plate 1 - Case 66
1(a) Shows gastric mucosa attended by severe chronic active inflammation with numerous lymphoid aggregates. Intestinal metaplasia and atrophy are also present. 1(b) shows numerous cocci within the apical mucus (red arrow) staining with Giemsa but not morphologically consistent with *H. pylori.* On use of immunohistochemistry 1(c), bacilli stain readily (green arrows) within the mucus. (Positive control inset)





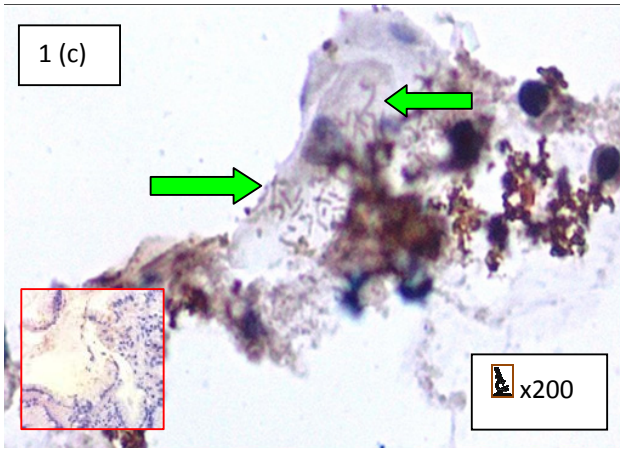
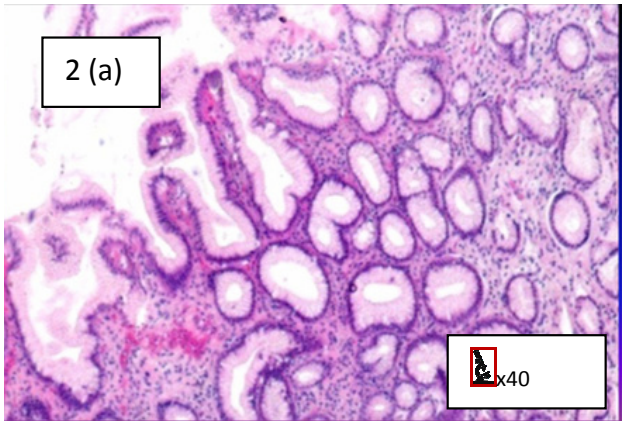
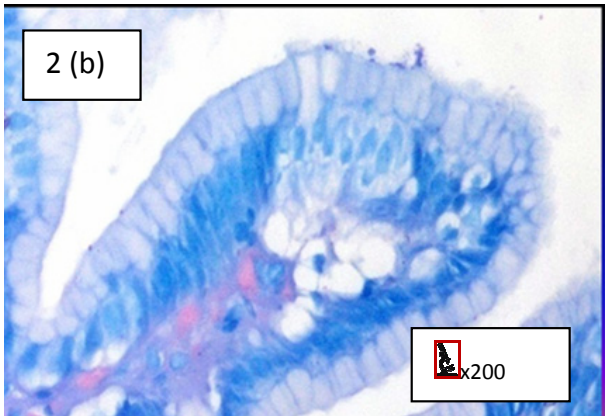
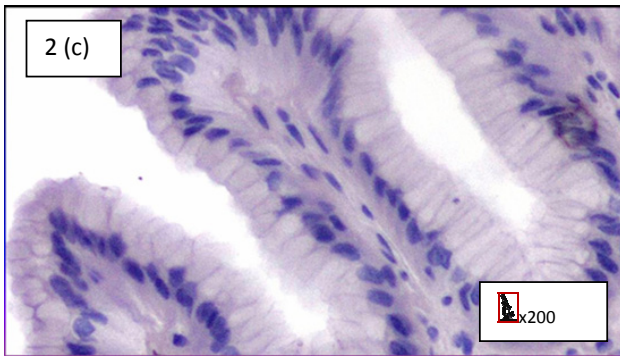


Figure 3: Plate 2 - Case 10
2 (a) Shows gastric mucosa exhibiting severe chronic inflammation. *H. pylori* is negative on both Giemsa 2 (b) and immunohistochemistry 2 (c)







DISCUSSION

Helicobacter pylori infection is a common cause of gastritis worldwide. Since its discovery by Marshall and Warren, various tests have been developed to diagnose infection. Histopathologic assessment is reliable in detection of the infection and assessing the inflammatory changes that occur in gastric mucosa thereof. Special stains continue to prove vital in visualizing the bacilli and coccoid forms of the bacteria. In this study, samples were selected from February 2016 to May 2017. Thirty prospective cases were collected from August

2016 to May 2017. All the selected archived blocks had sufficient amount of the sample to carry out the three staining techniques. For the prospective samples, processing was carried out as per the laboratory's standard protocols. A total of 89 biopsies that had been diagnosed with chronic gastritis without *H. pylori* infection were selected for review. The youngest patient was 7 years old and this was the only paediatric case (below 12 years of age). The dearth in the number of paediatric samples submitted to the laboratory should be a cause for concern. This is because it has been shown that there's a higher rate of *H. pylori* infection in the paediatric population in both developing and developed nations[3,4,12]. This may have affected the overall outcome of positive cases in the immunohistochemistry staining.

The most common endoscopic finding on visual exam was normal mucosa in 25 (32.1%) cases. Gastritis was present in 19 (24.4%) cases while duodenitis was present in 2 (2.6%)cases. Gastric ulcers and duodenal ulcers were seen in 10 (12.8%) cases and 6 (7.7%) cases respectively and were common in males. However, none of the samples had been collected on endoscopy as per the recommendations of the Updated Sydney classification system[9]. Therefore, there was a limitation in overall determination of the site of the gastritis requiring use of a modified data entry tool[13]. Haematoxylin and Eosin staining easily demonstrated the gastric mucosal changes that occur when the chronic infection is likely present. Of these changes, 64 (82.1%) biopsies demonstrated chronic inflammation without activity. Chronic active inflammation, severe inflammation and eosinophilic infiltration were present in 14 (17.9%), 39 (50%) and 13 (16.7%) cases respectively. These are pointers to recent infection. Eosinophilic infiltration is commonly encountered in children with gastritis. This may occur both in *H. pylori* gastritis and food allergy[14]. However, in the one paediatric case in this study, no eosinophilic infiltrate was noted. There likely was a different cause of the inflammatory response which requires further investigation. One case demonstrated both Cryptosporidic gastritis and *H. pylori* gastritis. This is likely to occur in the setting of immunosuppression[15]. Peptic ulceration was associated with a higher degree of severity of inflammation (+2 and +3). Only one case showed mild inflammation. In patients with non-ulcer dyspepsia (gastritis and normal mucosa on endoscopy), there was a less severe inflammation seen on histopathologic evaluation. Analysis of the endoscopic findings with the severity of inflammation showed no statistical significance.

Immunohistochemistry is recommended when numbers of the bacilli are too low to detect on H&E and Giemsa stains. It also aids identify cocci in biopsies but aren't diagnostic of *H. pylori* infection on Giemsa stain[10]. Of the 78 cases selected for immunostaining, 20 cases (26.5%) were positive on examination. IHC showed a low degree of bacterial colonization (+1) in 85% (17 of 20) of biopsies that were positive. The presence of lymphoid follicles correlated well with positive staining ($p = 0.032$, O.R. 3.1). The severity of inflammation, presence of atrophy and intestinal metaplasia showed no significant correlation with IHC positivity. There are low detection rates where atrophic gastritis and intestinal metaplasia occur, which are unfavorable environments for colonization[13]. However, only one case that had numerous cocci seen on Giemsa stain turned positive on IHC. Based on a study done by Tajalli *et al*[10], mild inflammation showed poor detection rates on Giemsa staining (13.0%) whereas there was a higher detection rate of 42.6% on immunohistochemistry. In this study, mild inflammation didn't show IHC positivity in any of the cases. Moderate and severe intensities of inflammation had detection rates of 11.5% and 14.1% respectively. It has been shown that increasing intensity of inflammation shows better detection rates. On assessment of quality of staining of organisms and the background, a majority of samples had medium quality; despite use of a monoclonal *H. pylori* antibody. Only 1 of 20 (2.5%) cases showing IHC positivity had high quality of organism staining, while only 7 of 78 cases (9.0%) had high quality background staining. Use of Novocastra monoclonal antibody showed high quality staining of organism morphology and background in 75.6% and 95.8% of cases[16]. In this study, use of manual immunohistochemical techniques may explain why few cases showed good morphology. However, this is unclear if it affected the overall detection rates. By using heating method for antigen retrieval rather than trypsin, excessive background staining of epithelium and mucus can be overcome[17].

Failure to note presence of bacilli on special staining techniques where there are characteristic tissue inflammatory patterns has led to the quip; "seek, yet ye shall not always find." Therefore, *H. pylori* negative gastritis is considered an entity on its own that requires further investigation[18]. Some explanations for this scenario include the use of proton pump inhibitors (which may

decrease the numbers of bacteria and shift their populations from the antrum to the corpus), recent use of antibiotics (that may suppress the infection but not reduce the inflammation) and sampling error[13]. Other well-known reasons include presence of gastric atrophy and intestinal metaplasia which are adaptive mechanisms to chronic gastritis. In metaplastic areas, *H. pylori* is undetectable by either conventional or special staining techniques in the majority of cases, despite serologic evidence of infection. To reduce the rates of potential false negatives, it is recommended that adequate sampling from the lesser and greater curvatures is done, proton pump inhibitors be stopped two weeks before endoscopic testing and antibiotics should not be administered four weeks before testing.

A study done by Genta *et al*[18] explains other factors that result in *H. pylori* negative gastritis. They include other diseases of the gastrointestinal tract such as inflammatory bowel disease and infectious agents. A small proportion of patients who had a negative result, despite their biopsies showing characteristic inflammatory patterns, later showed positive staining on repeat endoscopy after a mean interval of 540 days. Therefore, further history, proper clinical evaluation and long-term follow up may be recommended for the patients in this study whose results were negative but still have symptoms of chronic gastritis.

CONCLUSIONS

Haematoxylin and Eosin (H&E) stain adequately displays the inflammatory and adaptive changes associated with *H. pylori* infection. Giemsa staining, when performed as per required standards, is the preferred technique to visualize *H. pylori* on gastric biopsies. Immunohistochemistry should be carried out when lymphoid aggregates are present in Giemsa negative biopsies. Gastric biopsies submitted to the laboratory have adequate tissue material for carrying out various staining techniques.

RECOMMENDATIONS

Immunohistochemistry should be introduced in the histopathology laboratory to detect *Helicobacter pylori* infection when Giemsa stain does not detect the bacteria. Gastric biopsy samples should be collected during endoscopy using recommendations from the Sydney system.

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CONFLICT OF INTEREST

None declared.

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Fatal sharp force injuries: an autopsy study

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ABSTRACT

Objective: This work aims at studying fatal Sharp Force Injuries (SFI) with extensive characterization of its victims, region of the body injured, organ damaged and other associated factors.
Materials and Methods: This is a review of all the fatal SFI seen and had autopsies performed on them at the police clinic, Benin City, Edo State, Nigeria.
Results: A total of 40 fatal SFI were seen, accounting for 4.1% of all medicolegal autopsies. The youngest victim was a 2 year old female and the oldest, a 73 year old female, with a mean age of 32.98 ±14.46. Males accounted for 82.5% of cases. Age groups 30-39 years and 20-29 years were mostly involved. Most of the victims were traders, students and farmers, while most of the assaults (35%) took place along the street or a road. Homicides accounted for 97.5% of the SFI, while stab wound was most commonly seen (52.5%). The 3 common sites of injury on the body in the order of occurrence were anterior chest wall, neck and upper back each accounting for 28%, 20% and 15% respectively. The lungs was the commonest organ damaged (36.7%). The heart and the major vessels of the neck were equally damaged and each accounted for 16.3%. The commonest consequence of SFI seen was haemothorax (40%). Fifty two point five percent of victims died within 24 hours of injury, while one male was the assailant in most cases (55%).
Conclusion: Fatal SFI are common in young males, occurred most often on the streets, are almost always homicidal and dominated by stab wounds. The chest and neck were mostly involved, with the lungs most commonly damaged, while many victims died within 24 hours of injury.

Key words: Sharp force injury, Stab wounds, Incised wounds, Homicides

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INTRODUCTION

Sharp Force Injuries (SFI) are damage to tissues or organs by the use of objects or weapons with sharp edges or pointed ends like chisel, barbed wire, box cutters, screw drivers, knife, dagger, nail, needle, spear, arrow, sword, machete etc. These types of injuries have been classified in various ways; however, there are generally three specific but related subtypes: Stab Wounds (SW), Incised Wounds (IW) and Chop Wounds (CW)[1-3]. SW are usually deeper than they are wide and usually occur when a pointed weapon is thrust at or into a victim, though occasionally it can occur when a stationary pointed object is impacted by a moving body. Most times the direction of force is perpendicular to the skin surface, though any angle may occur especially following a stabbing during a fight[1-3]. SW tend to reflect the shape of the object that caused the injury and can be of 3 types: punctured, penetrating and perforating[1-3], IW are most times longer on the skin surface than it is deep and are usually caused by sharp edged objects that has impacted the body in an approximately parallel direction to the skin surface[1-3]. CW present as hybrid type of injury (sharp and blunt force injuries), are usually caused by heavy objects with sharp edges like an axe head, hatchet, tomahawk, boat propeller or lawn mower blade. CW has a combination of incised appearance on the skin surface, associated abrasions, contusion and blunt trauma. Fracture of a nearby bone may also occur[1-3]. CW are usually seen on exposed parts such as head, neck, face, shoulders and extremities[3]. Various works have

reported fatal SFI and observed that it could be a major pattern used in committing homicide or suicide or could occur accidently[1-8]. Irrespective of the manner of death associated with SFI, the commonest regions of the human body involved are; chest, neck, abdomen upper and lower limb and head, affecting mainly the following organs and tissues; heart, lungs, major blood vessels of the neck, intestine, peripheral arteries like femoral and radial arteries, liver and kidney[1-8]. The common causes of death following SFI are exsanguinations (severe haemorrhage), vital organ injury, air embolism, secondary infections and pneumothorax[1-13].

A good number of authoritative works in relation to fatal SFI have already been done in different countries,[2,4-11] while only a few Nigerian studies[12,13] mentioned SFI as a component of homicidal deaths. This present work aimed at studying only SFI with extensive characterization of its victims and other associated factors with respect to the SFI event.

MATERIALS AND METHODS

This is a review of all the fatal SFI reported to the police clinic, Benin City, Edo State, Nigeria, from January 1st 2008 to December 31st 2012 and had autopsies performed on them. The autopsies were performed in various mortuaries in Edo State. The major sources of information reviewed were the autopsy registers and reports of the police clinic. Their demographic features (age, sex), occupation of victims, scene and time of event, type of SFI, body region injured, organ damaged, mode of death, cause and manner of death were analysed statistically using SPSS version 17 (Chicago, Illinois) and P-value of <0.05 was considered as significant. Ethical clearance was given by the ethics and research committee of the Police Clinic.

RESULTS

A total of 40 fatal SFI were seen, accounting for 4.1% of all medicolegal autopsies. The youngest victim was a 2 year old female and the oldest, a 73 year old female, with a mean age of 32.98 ±14.46. Males accounted for 82.5%, while females accounted for 17.5% of cases in a male to female ratio of 4.7:1. Age groups 30-39 years and 20-29 years were mostly involved. No victim was aged between 50-59 age groups, as shown in figure 1.

Figure 1: Age and sex distribution of cases

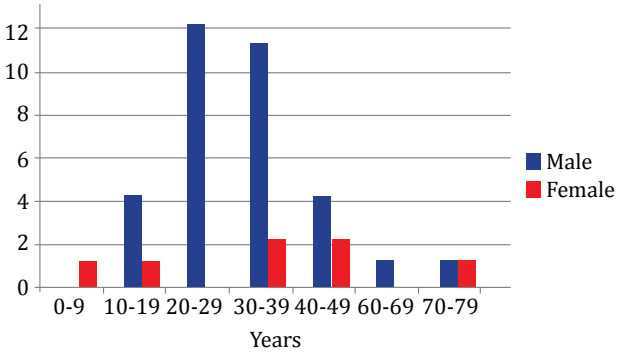


Table 1 shows the occupation of victims with trading, schooling and farming been the major occupations, accounting for 22.5%, 15% and 15% respectively. Most of the assaults took place along the street or a road (35%), closely followed by 27.5% of SFI that occurred in the victims house. Majority of fatal SFI occurred during late evening/ night periods (42.5%).

Based on manner of death classification, 97.5% of the SFI were homicides, while stab wound was most commonly seen (52.5%). Among the stab wounds, 90.9% of them were penetrating type of stab wounds. Single SFI wound was seen in 67.5% of cases. Two or 3 SFI wounds were seen in same number of cases, each accounting for 10%.

Table 1: Sociodemographic characteristics of victims

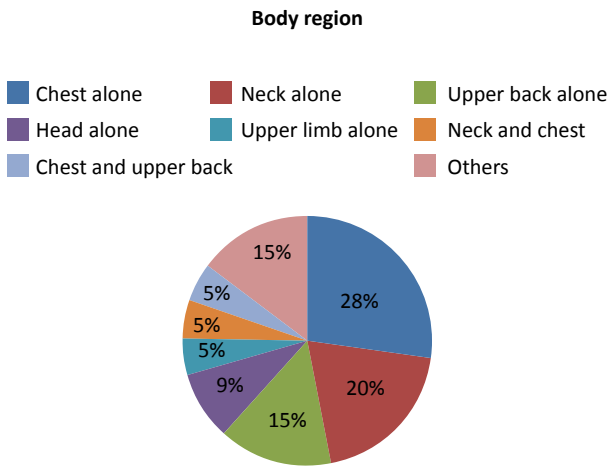
Characteristics	Frequency	(%)
Occupation (available for 36)		
Trading	9	22.5
Student	6	15
Farming	6	15
Driver	4	10
Artisan	4	10
Applicant	2	5
Others	5	12.5
Scene of event (available for34)		
On the street	14	35
Victims house	11	27.5
Bar / party venue	5	12.5
Farm	2	5.0
Others	2	5.0
Time of event (available for 38)		
Morning period	8	20
Afternoon period	2	5
Late evening /Night period	17	42.5
Mid night	4	10

Table 2: Medico legal characteristics

Manner of death	Frequency	(%)
Homicide	39	97.5
Accident	1	2.5
Number of wounds		
1	27	67.5
2	4	10.0
3	4	10.0
5	3	7.5
10	1	2.5
13	1	2.5
Nature of injury		
Incised wound	15	37.5
Stab wound	21	52.5
Chop wound	3	7.5
Incised/stab wound in a case	1	2.5
Stab wound type		
Punctured	2	9.1
Penetrating	20	90.9

The three common sites of injury on the body in the order of occurrence were anterior chest wall, neck and upper back each accounting for 28%, 20% and 15% respectively as shown in Figure 2.

Figure 2: Body region injured in victims of fatal SFI



The lungs was the commonest organ damaged (36.7%). The heart and the major vessels of the neck were equally damaged and each accounted for 16.3%. Peripheral limb vessels were damaged in 12.2% of cases as shown in Table 3. The commonest consequence of SFI seen was haemothorax (40%).

Table 3: Type of organ / tissue damaged and consequences in victims

Organ	Frequency		Consequences	Frequency	(%)
Lungs	18	36.7	Haemothorax	16	40
Heart	8	16.3	Haemoperi-cardium/ haemothorax	9	22.5
Major vessels of the neck	8	16.3	Massive external bleeding	3	7.5
Periph-eral limb vessels	6	12.2	Massive external bleeding	3	7.5
Brain	3	6.1	Intracranial bleeding	2	5
Liver	2	4.1	Hemoperito-neum	2	5
Others	4	8.3	Others	3	7.5

Table 4 shows the mode of death and the period of survival before death. Exsanguinations accompanied with vital organ injury (lungs and heart) were seen in 52.5% of cases, while exsanguinations due to injuries to major neck vessels and peripheral vessels accounted for 35% of deaths. Fifty two point five percent of victims died within 24 hours of injury and the common history was that on arrival in the hospital, the victim was confirmed death; however, in 35% of cases, the victims died on the spot following the assault.

Table 4: Mode of death and period of survival before death

Mode of death	Frequency	(%)	Survival Period	Frequency	(%)
Exsanguina-tions with vital organ injury	21	52.5	Available for 37 cases		
Exsanguina-tions	14	35	Death within 24 hours	21	52.5
Brain injury	3	7.5	Death on the spot	14	35
Septicaemia	1	2.5	Survived beyond24 hours	2	5
Paralytic ileus	1	2.5			

A single male was the assailant in most cases (55%), while SFI caused by a group of men was seen in 25% of cases. Only in 1 case was a female the assailant, as shown in table 5.

Defense wounds were seen in only 3 victims (7.5%). Two of them, had them on the posterior surface of their hands, while the 3rd had them on the forearm.

Table 5: Assailant sex distribution

	Available for 33	(%)
Single male	22	55
Single female	1	2.5
Group of men	10	25

Figures 3-5 show different types of SFI.

Other organs damaged include 2 cases of intestinal stab wounds and a case each involving the kidney and thoracic aorta. Other consequences include a case of peritonitis, sacral fracture with hemoperitoneum and upper limb (radius) fracture.

Figure 3: A case of chop wound caused by axe (initially as a linear laceration of scalp and showing skull fracture beneath).

Figure 4: A,B. Stab wounds to left upper chest area, with laceration of the left lung. C. Stab wound to the right posterior upper neck.

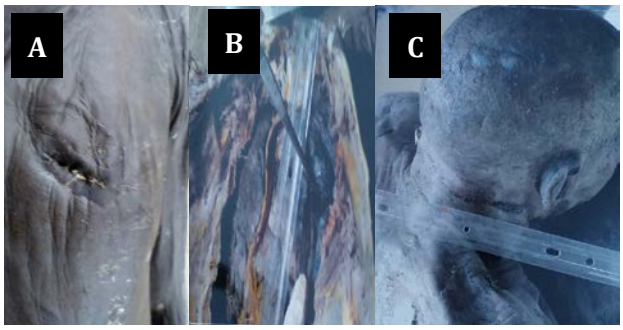
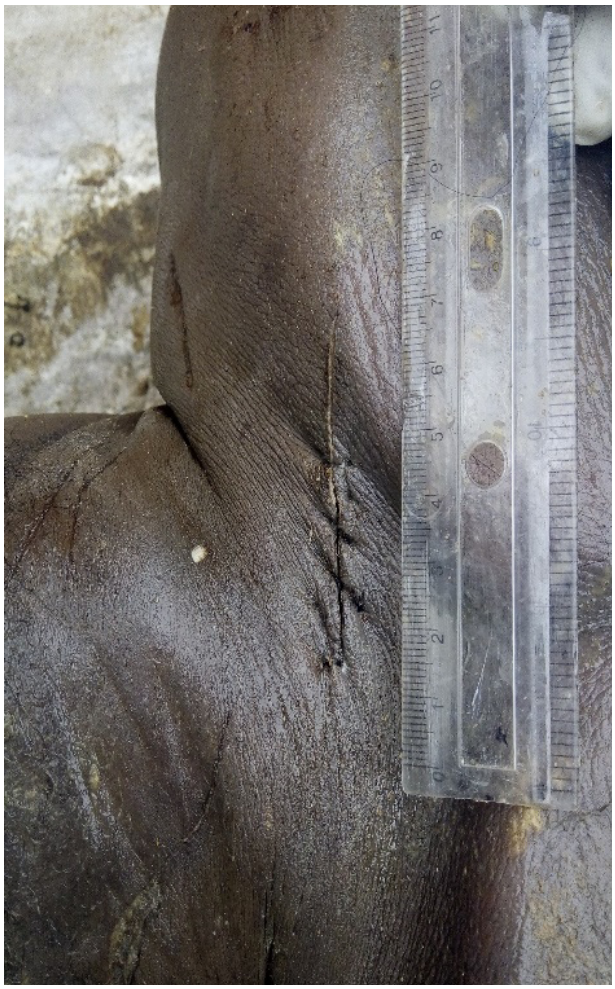


Figure 5: An incised wound at the deltoid region



DISCUSSION

Fatal SFI are not rare occurrences and have occurred since human existence as it was even recorded in the Bible: "Phine has the son of Eleazar…took a javelin in his hand and went after the man of Israel into the tent and thrust both of them through, the man of Israel and the woman through their body." Numbers 25:7-8. The rate of 4.1% in this study is close to 4.4% observed in Karachi; Pakistan, but less than 1.3% reported in Jamaica[9,10]. The reasons for this similarity and disparity cannot be readily explained because this index study covered a period of 5 years, the study from Pakistan was for 1 year, while in Jamaica, it was over a period of 17 years, though both studies recorded a higher number of medicolegal deaths than the index study.

Males far outnumber female victims of SFI. This is similar to previous observations[2,5-8,9,11]. More than half of the victims were within the age group 20-39 years , with a mean age of 32.98 ± 14.5. This agrees with findings in Texas, Jamaica and both Karachi and Sukkur, (Pakistan)[2,9-11]. Reasons for this include: desire for revenge, lack of patience, alcohol use, bad accomplices, disobedience and taking law in their hands etc, which are commonly seen among young males, while lower incidence in females are mainly attributed to custom, social values and practice of females to stay indoors[14].

Low socio economic levels, illiteracy, unemployment, unskilled workers, semi-skilled workers and unavailability of firearms are associated risk factors for both victims and assailants[14,15]. Most of the SFI victims in the index study were of low socioeconomic status, majority been petty traders, farmers and drivers. Students killed in rival cult fights also accounted for a significant proportion of victims.

Fatal SFI and homicides generally are mostly committed at night, mainly due to lower risk of identification in the darkness, chance of confrontations during day, abuse of alcohol and other substances at night[14]. Though the assailants were not interviewed to know their reason for choice of time to strike, the aforementioned reasons may also apply to the index study since 42.5% of cases occurred during late evening and night.

There is no consensus about the scene (indoors or out door) where the victim was injured. About 57.5% of cases in the index study occurred outdoors. In a Scandinavian study, females SFI occurred more in the victim's home, while more males were involved outside their homes[7]. In Southern India and Greece, outside the house of the victims (outdoors) was more common[14,16]. The fact that males are more frequently involved and are more outgoing than females may be reason. In contrast, in Canada, indoor occurrence is more common[17].

Based on manner of death categorization, death in SFI can be homicides, suicides or accidents[1-8]. All but one fatal SFI were homicides in the index study. This is similar to reports from Karachi; Pakistan which observed that all their cases were homicides[10]. Studies from more developed countries; Texas and New York (both in USA)and Italy observed more suicidal and accidental SFI[2,4,5]. A common fact from all studies was the fact that at least 70% of all fatal SFI were homicidal in nature[2,4,5,10]. Suicidal SFI accounted for 12-21% of all fatal SFI, while accidental causes were least. Complete lack of suicidal cause of fatal SFI in this series is not surprising because suicides are generally rare in our environment despite the abundance of suicidal risk factors[18].

Majority of fatal SFI victims (67.5%) received one SFI and it turned out to be fatal. This is slightly higher than 58% reported by Ormstad *et al* in Sweden, but higher than 34% observed in New York and far higher than 18% reported in Sukkur; Parkistan, where majority of their victims (82%) had multiple injuries[4,11]. Reports from Texas observed an average of 3.3 wounds per case. 2A relationship has been observed between the number of SFI wounds and the relationship of the assailant to the victim. The presence of more than 10 wounds are correlated to a close relationship between assailant and victim and to assailants with mental illness[6,8]. Between two and nine wounds were often seen in cases where the homicide was part of a fight among persons with lesser degree of relation, while a single SFI was often seen in cases where both the assailant and victim were alcoholics[6,8]. The relationship between the victim and the assailant was not recorded in the autopsy or police reports reviewed, however only 1 case of a female assailant was reported, while in 55% of cases, a single male was the assailant. This agrees with findings in Sweden that almost all assailants were males[6,8]. The presence of multiple wounds and by extension involvement of multiple sites are believed to be due to firm determination on the part of the assailant to be very sure that the victim is dead or will not recover later on[14]. In addition, involvement of multiple assailants or just because the victim goes on fighting for a longer duration cannot be ruled out[14].

SW was the most common wound seen (52.5%), with 90.9% of them been penetrating

type of SW. This is in agreement with previous studies, though in this index study, the rate is less than 93%, 91.3% and 60.9% reported in New York, Jamaica and Karachi respectively[4,9,10]. The high frequency of SW over IC and CW may be due to readily availability of weapons that cause SW in the environment and their ease of usage over tools like machete and axe that normally cause IC and CW in our environment. Cut throats and decapitations are more common in Karachi, as no single case of decapitation was seen in our series.

The chest was the most common region struck. The upper posterior back, which still presents the same risk as the chest also accounted for a significant proportion of region of the body injured. (Both regions accounted for 42.5%). This is similar to 42.1% observed in Jamaica, less than 58% reported in New York and higher than 20% and 16.4% observed in Pakistani studies[4,9,10,11]. Abdomen was the commonest site in Karachi and the second most common sites in Jamaica and Sukkur[9,10,11]. This is a sharp contrast to our findings. The abdomen was involved in only 3.6% of our cases. The neck region was the second most common body region injured in this series, which was the same observation in Karachi[10]. What influences the choice of the body region to be injured is not clear, however that assailants aim to kill or cause great destabilization and harm may not be ruled out.

The lungs were the single most damaged organ, distantly followed by the heart. This is different from the previous works, which documented intestine (Karachi) and heart (New York and Jamaica) as the most damaged organs[4,9,10]. Deaths due solely to SFI of the lungs are known to be less common[19]. Reason why it is the most injured organ in the index study is not known. Most fatal SFI especially SW to the chest are located in the left chest region, especially if the intention is to kill, because that is where the heart is located[19]. SW to the lungs typically occur from injuries on the front of the chest, less commonly from the sides and occasionally the back[19]. Exsanguination with massive haemothorax and occasional pneumothorax are usually the cause of death following SW to the lungs[19]. Due to high rate of involvement of the lungs, haemothorax was the most common consequence, in this series.

Penetrating cardiac injury is a dramatic and lethal form of trauma. The majority of patients will die before reaching medical care[20]. The risk of death is not dependent on the number of cardiac wounds whether single or multiple, rather the mortality is dependent on mechanism of wounding, cardiac chambers involved and possibly the presence of cardiac tamponade[20,21]. The heart was the 2nd most frequently injured organ in this study. Different studies reported various frequencies of heart involvement, it was the most injured organ in New York and Jamaica studies[4,9,10]. Deaths due to SW to the heart are usually due to a combination of haemothorax, external blood loss and haemopericardium[19].

Injuries to major vessels of the neck, following SFI to the neck, were seen in 16.3% of cases. Rapid death following SFI to the neck may be due to exsanguinations, air embolism or asphyxia (due to massive soft tissue haemorrhage with compression of the trachea and vessels of the neck)[19]. At times severing both major vessels and trachea may result in massive haemorrhaging into the respiratory pulmonary tract[19].

Defense wounds can be passive or active, are highly suggestive of homicides and are usually sustained in a bid to defend one's self from assailants[1,3,19]. These are usually located on the upper limb as seen in this study and are rarely located on the lower limb. The rate of 7.5% in the index study is too small compared to 31% in Texas, 33% in Southern India, 49% in New York and 75% in Sukkur; Pakistan[2,4,11,14]. The reasons for the low number of defense wounds are not clear. A study in Southern India, gave the following as the reasons for absence of defence wounds; involvement of multiple assailants, assault during sleep or intoxication and unexpected attack[14].

The major limitations of this study were incomplete routine documentation of parameters related to the injuries, documentation of weapons used and interviewing the known assailants to understand their socio demographic characteristics and intentions.

In conclusion, fatal SFI in our setting commonly involve young males, occurred more on the streets, are almost always homicidal and dominated by SW. The chest and neck were mostly involved, with the lungs being most damaged. Many victims died within 24 hours of injury.

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Angiosarcoma arising from a haemangioma of the nasal cavity: a case report

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ABSTRACT

Angiosarcomas are malignant tumours of vessels particularly endothelial cells. Angiosarcoma is an aggressive tumour that often involves soft tissues and the head and neck. Angiosarcomas are divided into those with lymphoedema and those without. Those without lymphoedema occur in the head and neck especially the scalp. Sinonasal angiosarcomas account for approximately 1% of sarcomas. Angiosarcomas arising from hemangiomas of the nasal cavity are extremely rare. Angiosarcomas of the nasal cavity have a better prognosis than soft tissue angiosarcomas. The 5 year survival rate is 22% compared to 12% in soft tissue angiosarcomas. The aim of this case report is to close the knowledge gap on angiosarcomas of the nasal cavity especially in Africa. There is no standard treatment for nasal cavity angiosarcomas. However, there are reports of surgery with wide excision margins free of tumour combined with radiotherapy.

A case of a 16 year old female who presented with right nasal blockage, epistaxis and anosmia for 2 months is reported. On examination there was purulent rhinorrhea, a posterior nasal drip and a mass that bled easily. The left nose was normal. A biopsy was taken and revealed dilated vascular channels with prominent endothelial cells. There were also areas with capillaries with tufted endothelial cells resembling a haemangioma. The tumour was infiltrative without mitoses or atypical mitoses. There was haemorrhage and necrosis. There was respiratory epithelium and anastomosing vascular channels. No tumour cell spindling. There were no intracytoplasmic vacuoles, extravasated red blood cells or eosinophilic hyaline globules. The patient underwent a rhinotomy and was discharged in good condition. There are 27 case reports of angiosarcomas of the nasal cavity alone globally to date and there are a total of 70 case reports if combined angiosarcomas of the nasal cavity and paranasal sinuses are included.

Angiosarcoma arising from a haemangioma of the nasal cavity is a rare tumour. The condition has not previously been reported in Africans. Case reports from Africa are encouraged in order to have an accurate assessment of the epidemiology of the condition.

Keywords: Angiosarcoma arising from a haemangioma, Nasal cavity, Case report

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INTRODUCTION

Angiosarcomas are malignant tumours of vessels particularly endothelial cells. Its synonyms include epitheloid haemangioendothelioma, haemangioblastoma, haemangiosarcoma, lymphangiosarcoma, malignant haemangioendothelioma, malignant angioendothelioma. Angiosarcoma is an aggressive tumour that often involves soft tissues and the head and neck. Angiosarcoma is divided into those with lymphoedema and those without. Those without lymphoedema occur in the head and neck especially the scalp[1]. Sinonasal angiosarcomas account for approximately 1% of sarcomas[2]. Angiosarcomas arising from a haemangioma of the nasal cavity excluding paranasal sinuses are extremely rare. Angiosarcomas of the nasal cavity have a better prognosis than soft tissue angiosarcomas in which most patients don't survive for 2 years[1]. The 5 year survival rate is 22% compared to 12% in soft tissue angiosarcomas. The survival rate also depends on the grade of differentiation of the tumour and the stage at diagnosis. Well differentiated tumours have a better prognosis than poorly differentiated tumours. Low stage tumours tend to do better than high stage tumours[2-4].

CASE REPORT

A case of a 16 year old female who presented with right nasal blockage, epistaxis and anosmia for 2 months is reported. On examination there was purulent

rhinorrhea, a posterior nasal drip and a mass that bled easily. The mass was soft and haemorrhagic and measured 3.0x2.0x1.5cm and filled the right nasal cavity. The left nose was normal and the paranasal sinuses were free of tumour. She was mildly ill and was not bedridden. A biopsy was received in the Pathology Department which comprised of haemorrhagic tan soft tissue measuring 2.1x1.0x0.5cm. The cut surface was soft with cystic spaces. Microscopy revealed dilated anastomosing vascular channels with prominent endothelial cells (Figures 1 and 2).

Figure 1: A dilated vascular channel representative of the numerous other channels in the specimen X20. The prominent endothelial cells are visible even at this magnification

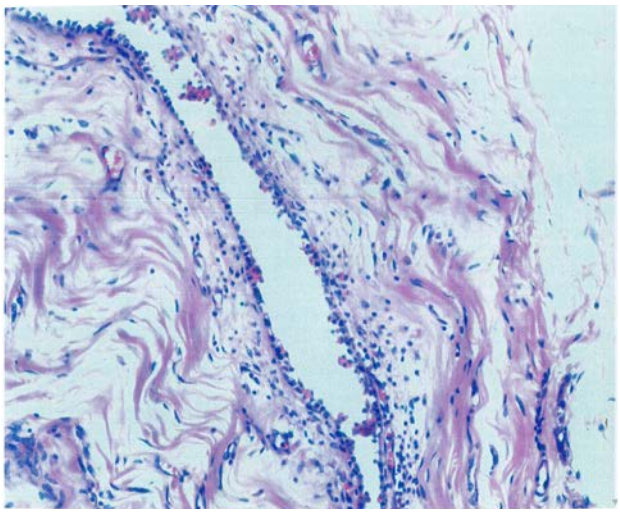
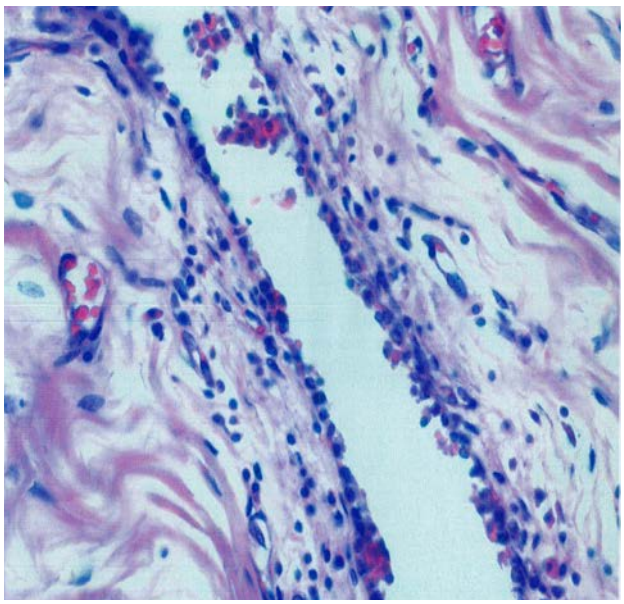


Figure 2: The dilated vascular channel has prominent atypical endothelial cells which is different from flat inconspicuous endothelial cells seen in normal vessel X40



In addition there were exuberant masses next to the channels that consisted of capillary proliferations with tufted endothelial cells resembling a haemangioma (Figures 3 and 4). Angiosarcomas with a haemangioma are considered to arise from the haemangioma. The degree of atypia was mild and there was no pleomorphism, thus a low grade tumour. Other pathology findings included infiltrative tumour without mitoses or atypical mitoses. There was haemorrhage and necrosis. There was respiratory epithelium and anastomosing vascular channels. No tumour cell spindling. There were no intracytoplasmic vacuoles. Extravasated red blood cells and extracellular eosinophilic hyaline globules were absent. Inflammatory cells were present. The patient underwent a right rhinotomy and the mass was removed with free surgical margins. The patient was discharged in good condition.

Figure 3: The peculiar capillary proliferation with tufted endothelial cells. There is minimal atypia except for the tufting thus resembling a haemangiona X20

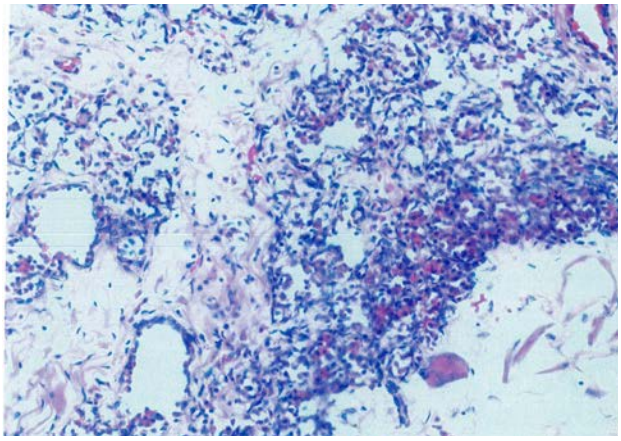
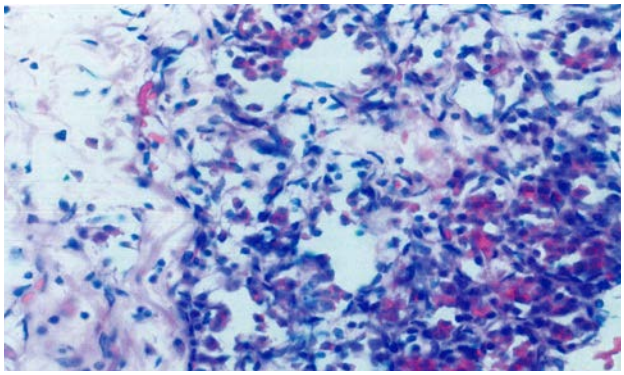


Figure 4: Higher magnification showing the tufted endothelial cells. There is no pleomorphism. These areas are inseperable from haemangioma except for the tufting of endothelial cells which is more prominent X40



Angiosarcomas are graded predominantly according to the cytologic atypia of the endothelial cells. So patients with low grade angiosarcomas have an excellent prognosis whereas high grade tumours have a poor prognosis[5,6]. de Melo *et al*[7] found a patient alive after 4 years on treatment although with multiple recurrences. Nasal angiosarcomas are common in males and occur in the middle age. Females tend to be younger at presentation. Most of the tumours are low grade[8]. Although angiosarcomas of the nasal cavity have a good prognosis, there have been anecdotal reports of metastases to the larynx[9]. As far as aetiology is concerned angiosarcoma is associated with radiation exposure, arsenic, vinyl chloride and thorotrast[10].

There is no standard treatment for nasal cavity angiosarcomas. Ninety seven percent of studies reported wide resection with margins free of tumour and radiotherapy (4000 – 5000 rads) as the treatment of choice. Tumour recurrence is because of incomplete excision. Chemotherapy has a limited effect although there have been reports of success with recombinant interleukin 2 combined with surgery and with placlitaxel [3,7,10].

The nasal cavity is considered separate from paranasal sinuses in the International Code of Disease-10 (ICD-10)[11]. There are 70 case reports of angiosarcomas of the nasal cavity and paranasal sinuses. Out of these 43 have a combined involvement of the nasal cavity and paranasal sinuses [2,3,8,9,12-15]. These case reports were from Europe, Asia, Australia and America. There are no case reports from Africa. Overall there are 27 cases of angiosarcomas of the nasal cavity alone.

DISCUSSION

Our patient was a young female which makes her condition rare since angiosarcomas of the nasal cavity are commoner in middle aged males[8]. In addition angiosarcomas arising from haemangiomas are rare in African patients where the condition has not been reported. The presentation of the patient with nasal blockage and a mass in the nasal cavity is the same as in other case reports. The patient was mildly ill. This is attributed to the low grade of the tumour. The low grade tumour is also the commoner presentation of angiosarcomas of the nasal cavity. The tumour was also less than 4 cm which has a better prognosis.

Regarding the histopathology, the dilated vascular channels and prominent endothelial cells are typical of angiosarcomas and different from ordinary vessels which have flat endothelial cells. The subjacent capillary proliferation has previously been reported and was responsible for the misdiagnosis as a haemangioma[2]. The diagnosis was arrived at based on the Haematoxylin and Eosin stains. No immunohistochemical stains were used since vascular markers have variable sensitivity and one study found no correlation between CD31 and CD34 staining in angiosarcoma thus requiring a panel of antibodies which was not affordable. Besides the vascular markers would not help in distinguishing angiosarcomas from haemangiomas which are also positive for vascular markers[16,17].

The patient underwent surgery only as the method of treatment. Since the mode of treatment is not standard, surgery alone with wide surgical margins may prove to be beneficial. Our case report resembles previous case reports with similar signs and symptoms. This means that the African patient is not unique and can be included in the global epidemiologic profile.

The differential diagnosis includes haemangioma especially a pyogenic granuloma, a biphasic composite haemangioendothelioma but this has intracytoplasmic vacuoles, however, the dilated vascular channels are not seen in haemangiomas. A nasopharyngeal angiofibroma in this age group may mimic an angiosarcoma, however, they have a fibrous connective tissue stroma and the endothelial cells are not atypical. A haemangiopericytoma may have vascular channels but these have a "staghorn" appearance. Kaposi's sarcoma may present with slit-like vascular spaces which seem to dissect through the tissue, however, bland spindle cells and eosinophilic globules are often seen. An arteriovenous malformation may have vascular channels but does not have interanastomosing or endothelial atypia. Other differentials include epitheloid haemangioma, intravascular papillary endothelial hyperplasia (Masson's tumour), angiomatous polyp, angiomyolipoma and vascular leiomyoma, however, these conditions lack anastomosing channels and endothelial atypia.

Ancillary studies include immunohistochemistry. Angiosarcomas are positive for Factor VIII-Related Antigen, the most specific marker. They are also CD34, CD31 and Vimentin +ve. They are negative for HHV-8 seen in Kaposi's sarcoma and desmin seen in vascular leoimyoma. They are focally reactive with keratin or epithelial membrane antigen and actins[15]. Other studies include molecular studies or cytogenetic studies which reveal complex structural chromosomal abnormalities such as deletions and additions of chromosomes[1,3,4,9,14,16,17,18,] loss of the Y chromosome and Trisomy[5]. DNA ploidy shows diploidy[18,19].

CONCLUSION AND RECOMMENDATION

Angiosarcoma arising from a haemangioma of the nasal cavity in this 16 year old is a rare case. This case report is the first from Africa. The histopathology revealed a low grade angiosarcoma with dilated vascular channels and prominent atypical endothelial cells. Other case reports from Africa are encouraged for a better assessment of the epidemiology of the condition.

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Hypereosinophilia caused by alveolar soft part sarcoma: Case report of autopsy findings

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ABSTRACT

Eosinophilia is an increase of above 0.5x 10^9/l of eosinophils in peripheral blood count. There are three levels of severity of eosinophilia. Hypereosinophilia refers to severity levels above 1.5x10^9/l. This is a case report of a five year old boy who presented with hypereosinophilia. Postmortem and histology confirmed diagnosis of alveolar soft part sarcoma. There are several conditions associated with hypereosinophilia. This article reflects peripheral eosinophilia as a unique presentation for solid tumours particularly alveolar soft part sarcoma.

Key words: Hypereosinophilia, Alveolar soft part Sarcoma, and Eosinopoietic cytokines

INTRODUCTION

Hypersinophilia is classified into three broad categories based on the cause mainly as clonal (primary), secondary (reactive) and idiopathic[1]. This categorization uses clinical presentation, morphological evaluation and molecular techniques. The primary eosinophilias are associated with haematological malignancies. The reactive eosinophilias are associated with a variety of causes which include malignant and non-malignant conditions[2]. The malignant causes of non-myeloid origin includes thyroid, genitourinary, gastrointestinal, breast carcinoma,lung adenocarcinoma, oat cell carcinoma and adenocarcinoma of the lung[3]. Persistence hypereosinophilia in the absence of known causes is considered a paraneoplastic syndrome and this is well documented in large cell carcinoma of the lung[4]. Eosinophilia may present an early para clinical sign of malignant disease and host anti-tumour effect. Eosinophilia is associated with increased risk of bladder cancer. The association and role of eosinophilia in some tumours has not been well established[5]. A rare case of alveolar soft part sarcoma of the thigh in a child presenting with hypereosinophilia is presented here.

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CASE REPORT

This was a five years, 4 months old child who presented with right hip weakness after a fall five months ago. External fixation was done with plaster of Paris which was removed a month later. During review, a swelling was noticed in the right thigh extending into the hip joint and abdomen. Complete blood count showed hypereosinophilia and radiological evaluation revealed erosion of the right iliac, pubic bone crest only sparing the ischium. Fine needle aspirate of the swelling suggested a histiocytic disorder. Bone marrow evaluation was reported as chronic myeloid neoplasm associated with hypereosinophilia. The treatment given was systematic high dose corticosteroid therapy, however the condition worsened and the child did not survive.

The autopsy examination of the child was done after discussion and assent from the parents. The body was of an African male child appearing the state age, well nourished, weight 19 kilograms, and height 105cm. The skin was angiodematous with pruritic marks. The head normocephalic without any abnormalities. The scalp hair short and dark. There was facial and bilateral pedal oedema, mild pallor and no lymph node involvement. The abdomen slightly distended with a mass in the right iliac fossa extending into the right thigh causing enlargement; circumference approximately 15cm larger than the normal left side. The chest, the back and other extremities were unremarkable.

The body was opened in the usual Y-incision pattern. The lungs and the heart were in the right location. The tracheobronchial tree had frothy fluid. The

lungs were well lobulated bilaterally.The lung was boggy and the parenchyma showed congestion. The heart was enlarged and globular with thrombosis in the right auricular appendages. The right and left ventricles were dilated. The ventricular walls slightly were enlarged.

The pelvis had a tumour arising from the right thigh extending into the iliac fossa retroperitoneal infiltrating the psoas muscles, adhering to the caecum displacing the bladder laterally. The tumour was large 15cm by 12cm by 9cm, weight 1400grams eroding and infiltrating the right pelvic bone, the ilium, pubis, sparing the acetabulum and inferior part of the ischiump. The femoral bone was not involved with the tumour. The cut section of the tumour was whitish pink soft with uniform consistency. Figure 1 shows the tumour arising from the pelvis and the cut section.

Alveolar soft part sarcoma hypereosinophilia

Figure 1a: Gross appearance of tumour in situ

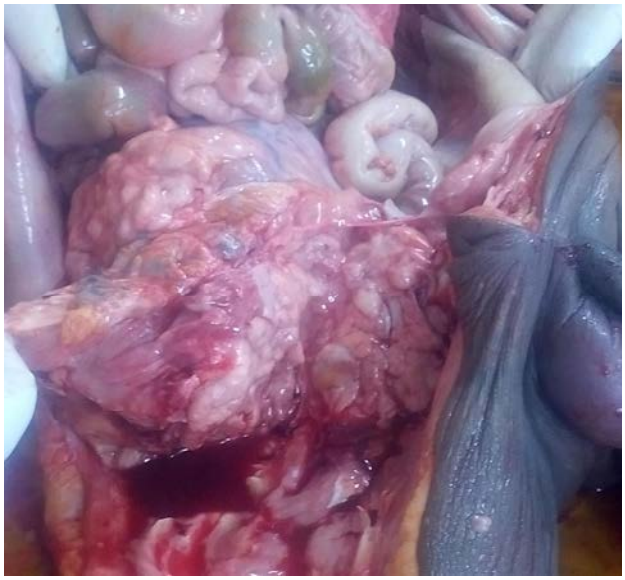
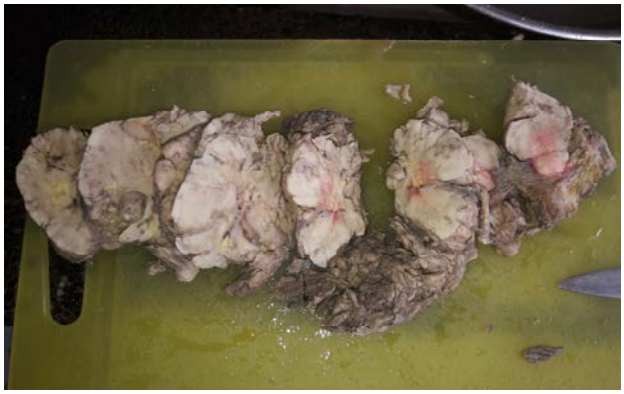


Figure 1b: Gross appearance of tumour

Before fixation with formaldehyde

Grossing after fixation

Figure 1c: Grossing tumour



The liver was enlarged, weight 1200grams, parenchyma uniform tan pink without nodules. The spleen weighed 560grams, the paraortic nodes were enlarged. The intestines had normal glistening surfaces, no luminal obstruction. The stomach, intestines, pancreas, kidneys, bladder and other viscera were unremarkable. The pelvic and femoral vessels were intact.

The brain was removed in the usual fashion by scalp incision. The dural and meningeal leaflets were normal. The gyral and sulci artichectural pattern was within normal limits on the frontal, parietal, occipital and base of the brain. The blood vessels formation and distribution, circle of willis was unremarkable. The brainstem, cerebellum and cranial nerves were unravelling. The parenchyma of brain cut into multiple showed cortical ribbon of uniform width without evidence of metastasic disease grossly.

The sections from the tumour dissected at multiple levels shows a tumour separated by nests of connective tissue septae forming alveolar pattern. Some are attached and others form flat forming pseudoglandular appearance. The cells are round to ovoid in shape with plump abundant granular acidophilic cytoplasm. Sections show nesting pattern of growth with predominant alveolar pattern. No multinucleate giant cells seen, no necrosis and abnormal mitotic figures. The pelvic bones were infiltrated with the tumour as well as the pelvic nodes. The possible diagnoses were alveolar rhabdomyosarcoma and alveolar soft part sarcoma. Figure 2 shows tumour staining with Hematoxylin and Eosin stain.

Figure 2: Haematoxylin and Eosin

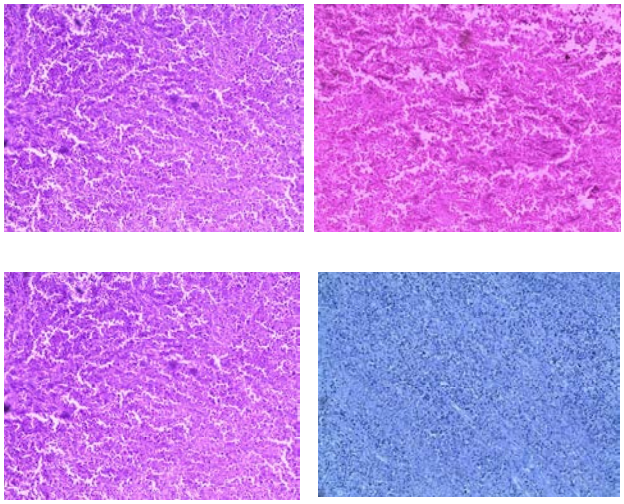
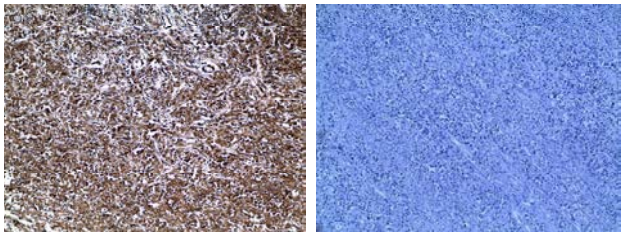


Figure 3 (Desmin weakly reactive and anti-smooth musle actin). The stains were used to differenciate the lesions with alveolar soft part sarcoma showing strong reactivity with anti smooth muscle actin and weak staining with desmin.

Figure 3: Special stains

Anti-smooth muscle actin positive

Desmin weakly reactive



The liver showed mild fatty changes, tissue eosinophilia and no metastasis. The spleen, lungs, the skin and the heart showed marked infiltration by the eosinophils. No metastasis to the brain, liver, spleen and the lungs. In conclusion, the immediate cause of death was congestive heart failure resulting from end organ damage to the heart caused by hypereosinophilia, the primary cause was solid tumour, alveolar soft part sarcoma.

DISCUSSION

Hypereosinophilia in solid malignancies are rare. Alveolar soft part rhabdomyosarcoma becomes enlisted among thyroid, hepatocellular, bladder carcinoma, lung adenocarcinoma, oat cell carcinoma, undifferenciated embryonal rhabdomyosarcoma, cardiac rhabdomyosarcoma anduterine leiomyosarcoma as tumours associated with hypereosinophilia[6]. The existence of hypereosinophilia without strong proof of allergic reaction, no leukemic process of the bone marrow favor a paraneoplastic process as in this patient. The histopathological examination of the tissues confirmed the tumour and extensive tissue eosinophilia potentially causing end organ damage to the heart and the lungs.

Alveolar soft part sarcoma is a rare distinct soft tissue sarcoma. It develops in younger people and accounts for 0.5 to 1% of all soft tissue tumours. Clinically, it appears to have an indolent growth pattern but surprisingly up to 79% develop metastatic disease with a high proportion resistant to conventional chemotherapy agents responsible for high mortality. In children the tumour occurs often in the head and neck region[6]. In adults the lower extremities are the most common location of the lesion. The most common metastatic sites are the lungs, liver and brain, the latter is considered a significant feature of alveolar soft part sarcoma[7].

The pathogenic mechanisms of reactive hypereosinophilia in tumours are controversial[8]. The common postulates are eosinophils have a role in tumour immunomodulation and that explains the good and poor prognostic outcomes in some tumours[9]. They are also biomarkers in some tumours and for instance high levels are a risk for development in bladder carcinoma. Tumours also produce eosinopoietic cytokines such as IL-5 and Granulocyte/Macrophage colony stimulating factors[10]. This is a double hit where the hypereosinophilia causes immediate severe complications to the organs and the tumour also progressively worsen the disease process. The heart is the most vulnerable to end organ damage with myocardial necrosis within weeks followed by valvular involvement, thrombosis and fibrosis. In the late stage, Loefffler's endocarditis and myocardial fibrosis manifest with congestive cardiac insufficiency, hypertrophy, dilation and pericardial effusion[11]. Surgical resection of tumours has a role in reducing hypereosinophilia. These features were present and increased the risk of anaesthetic complication making surgical role limited.

The molecular pathogenesis of alveolar soft part sarcoma plays a big role in the pathogenesis,clinical behavior and outcomes of this tumour[12]. Key to this is the unbalanced translocation between chromosome 17(ASPL gene) and chromosome X(TFE-3gene) resulting in formation of ASPL-TFE-3 fusion gene products which has an important role in the pathogenesis by activation of tyrosine kinase receptor, C-MET

and other pathways[13]. The current therapeutic approaches focus on the molecular mechanisms since surgical and convectional therapies have poor outcome[14]. Corticosteroids were administered without improvement and clinical condition was not favorable for surgery which anyway still has poor outcome.

Future studies in understanding the pathogenesis of hyper eosinophilia in alveolar soft part sarcoma should establish the link between its fusion gene products and the tyrosine kinase activators. The molecular studies were not done to determine these abnormalities. Comprehensive evaluation of the alveolar soft part sarcoma must include molecular studies for targeted therapy[15].

In conclusion, the presence of persistence hypereosinophilia should evoke evaluation with radiological, pathological and other techniques to rule out a tumour. This case is among the few articles of alveolar soft part sarcoma presenting with hypereosinophilia. The constrain of resources limited full immunohistological and molecular characterization of the tumour.

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Postmortem findings in a kidney graft transplant recipient with persistent febrile neutropenia: a case report

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ABSTRACT

Invasive fungal infections occur frequently in the setting of immunosuppression associated with therapy for haematological malignancies, haematopoietic stem cell transplantation or solid organ transplant. The infections are responsible for increased morbidity and mortality in post organ transplant like kidney. With introduction to organ transplant practice in the local setting, clinicians should consider fungal infections other than other bacterial causes in post-transplant cases. This is a case of fungal infection presenting with persistent febrile neutropenia in post renal transplant recipient.

This is autopsy report of a 61 year old male retired driver from rural Kenya who had end stage renal disease for 2 years with diabetes mellitus and hypertension. He was started on haemodialysis on September 2011 and later had kidney transplant on October 2013. Six months later, he was treated for persistent febrile neutropenia, developed subcutaneous swelling on the cervical region for two months, lower limbs and trunk which histopathology showed as aspergillosis and mucormycosis. During the course of treatment, he was diagnosed with cytomegalovirus, hepatitis B and later passed on the same year.

Fungal infections should be considered in patients with febrile neutropenia undergoing immunosuppressive therapy associated with organ-transplant and malignancies.

Key words: Febrile neutropenia, Renal graft transplant, and Invasive fungal infection

INTRODUCTION

Mucormycosis and aspergillosis are the most common invasive fungal infections that occur frequently in the setting of immunosuppression associated with therapy for haematological malignancies, haematopoietic stem cell transplantation or solid organ transplant[1]. The incidence of the infection varies with the type of organ transplant[2]. In kidney transplant, the incidence is 2 to 14% and the infections are responsible for increased morbidity and mortality[3]. The incidence of mucormycosis is 0.2-1.2% with a mortality of 60-100% whereas aspergillosis is associated with 0.5-2.2% and 88% mortality making combined infection very fatal[4,5]. The most common form of mucormycosis are the rhino cerebral and the pulmonary types[6]. The frequent pathological forms of aspergillosis are acute invasive aspergillosis and chronic necrotizing aspergillosis[7].

CASE REPORT

This report is a description of postmortem findings in a 61 year old J.G.M. who had diabetes mellitus and hypertension with subsequent end stage kidney failure and renal transplant. He developed cytomegalovirus infection and hepatitis B virus infection within the two years post-transplant period. Post transplantation therapy included oral mycophenolic acid, cyclosporine, prednisolone, isoniazid, lamivudine and mixed (30/70) subcutaneous insulin injection for the diabetes. The autopsy was done after consent. The body was of an African male descent of normal built and physique, height 172 cm and weight 79 kg. There were multiple subcutaneous swellings on the left parasternal and right anterior cervical region, left thigh and anterior abdominal wall. The posterior cervical nodes were enlarged and also had bilateral pedal oedema. On the chest wall

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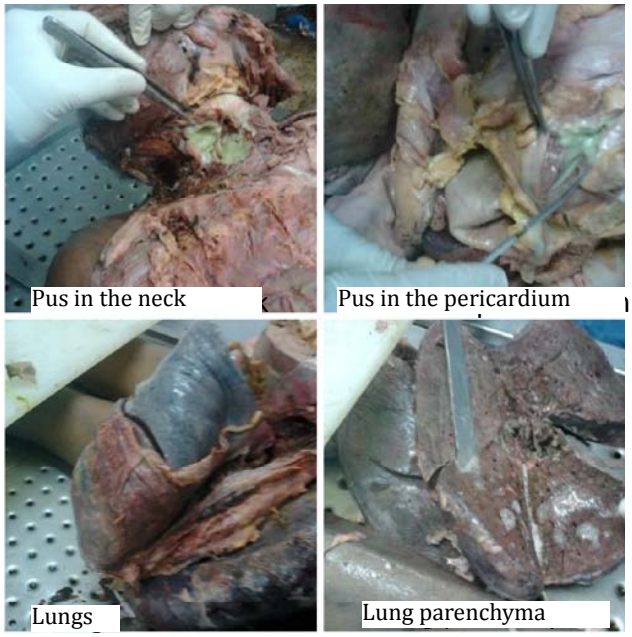
was a healing left sternal scar with a subcutaneous nodular swelling 2cm by 4 cm. The abdomen had a surgical scar in the right iliac fossa acquired during the transplant surgery. Musculoskeletal regions showed healed scars on the left anterior mid-thigh and nodular lesions on the left thigh.

The neck dissection revealed thick purulent exudate tracking along the carotid vessels and the trachea into the mediastinum along the pulmonary and aortic vessels into the pericardial sac forming pyopericardium. The same exudate covered visceral and parietal surfaces of the pleura and also on the lungs. The pleura was thick, greyish with the thick ceramic grey pus tracking into the chest wall connecting nodular lesions on the chest wall and cervical regions. The heart was enlarged, visceral pericardium thickened, covered with thick creamish grey pus (Figure 1).

Figure 1: Invasive fungal infection-aspergillosis and mucormurcosis in febrile neutropenia



The left ventricular wall was thickened. The atria, ventricular chambers and the valves were normal. Both lungs were darkened, the pleura was thickened, grey discoloration with adhesions. The parenchyma had mottled appearance of dark grey and red hepatization. There were also dark grey granules from the left upper lobe and thick dark pus like used engine oil appearance. The transplanted kidney on the left side was enlarged and the native kidney was shrunken. The liver was enlarged and congested. Notable was a cystic area well circumscribed by a pseudo-capsule with necrotic, suppurative content similar to the one in the pericardial sac. The gall bladder was unremarkable. The nodular lesions on the chest wall revealed thick creamish pus with similar gross appearance to the pus found along the mediastinum .

The brain was removed in the usual fashion by scalp incision. The dural and meningeal leaflets were normal. The gyral and sulci artichectural pattern were within normal limits on the frontal, parietal, occipital and base of the brain. The blood vessels and circle of Willis was unremarkable. The brainstem, cerebellum and cranial nerves were unravelling. The parenchyma of brain cut into multiples sections show cortical ribbon of uniform width. No evidence of inflammation grossly.

The histological assessment of the samples showed extensive inflammation on the visceral surfaces of the heart, lungs and carotid sheaths occasioned by the presence of inflammatory neutrophils, mostly degenerating, macrophages and lymphocytes. There were septate fungal elements with some acutely branching hyphae with other branching more than 90 degrees with necrotic debri (Figure 2).

Figure 2: Haematoxylin and Eosin

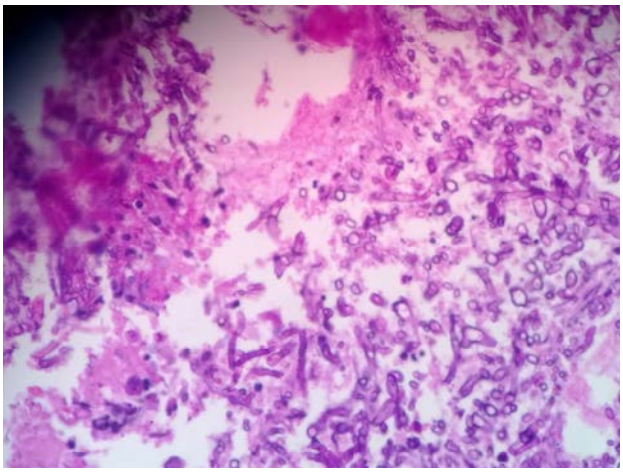
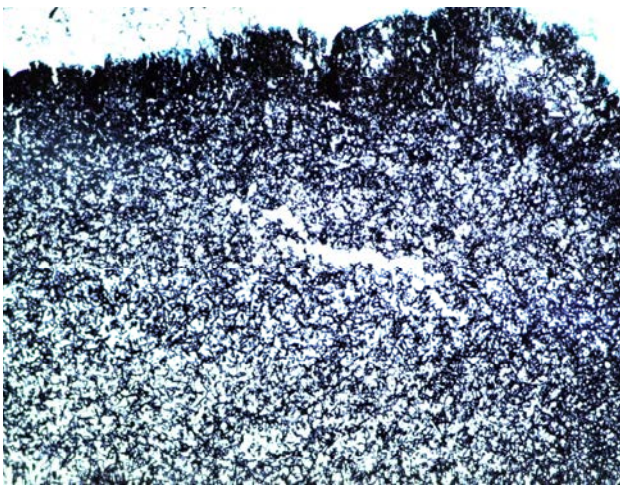


Figure 3: Groccots stain



Haematoxylin and Eosin stain and (Figure 3 Grocott's stain) the gram stain for the pus was negative and Ziel Neelsen Stain did not yield acid fast alcohol bacilli. Fungal culture grew aspergillosis species, no bacteria. There was mixed infections of aspergillosis and mucormycosis fungal species as concluded in the culture report. Subtyping was not done because of resource limitations. The cause of death was disseminated fungal infection due to immunosuppressive therapy in post renal transplant recipient.

DISCUSSION

Diagnosis of fungal infections in post-transplant recipients can be challenging because of the vague symptoms and lack of specificity of laboratory or radiological test[8]. One of the clinical indicators of invasive fungal infection and chronic rejection in renal recipients is elevated creatinine[9]. A combination of clinical tests and screening is necessary. It is estimated that 30% causes of death are invasive fungal infections. The incidence of fungal infection varies and depends on the transplanted organ. The mortality varies with the causative organism for instance aspergillosis is 40%, candidiasis 34% and cryptococcosis 27%. The onset of the infection varies with candidiasis having the earlies onset[10]. In this patient, the conclusive diagnosis was mixed aspergillus and mucormycosis fungal species infection which combined has mortality causing demise within a year. In most instances, the diagnosis is made at autopsy after ancillary histological and microbiological investigations.

Any post-transplant patient should be assessed for risk of infection which depends on the host factors and the environment. Aspergillus spores occur in the environment. Infections can occur within or after 90 days depending on risk factors[11]. Overall, risks for infection with invasive aspergillosis include renal failure after surgery, diabetes, age above 50 years, prolonged pre-transplant dialysis, chronic impaired graft function, immunosuppressive therapy, repeated bacterial infection, cytomegalovirus infection and leucopenia[12]. All these risks were found in this patient. The site of infection beyond the respiratory tract includes the skeletal system, thyroid, skin and central nervous system. These are frequently due to dissemination from a primary respiratory tract site. The postmortem examination revealed lesions in the lungs, pericardium and tracking to the carotid sheath and neck structures.

Early diagnosis is key in initiating treatment before life threatening complications. Invasive procedures that provide material for microcopy and culture should be done early if these infections are suspected. However, diagnosis of invasive aspergillosis can be challenging and frequently require histological evidence for infection and culture[13]. Culture remains an important modality for identification of aspergillosis to the species to provide important clues to antifungal susceptibility and pathogenic potential of the organism identified aspergillosis tends to grow well on routine media, but yields can be increased with fungal media such as Sabouraud's dextrose agar. Specimens that are obtained from nonsterile sites should be cultured in the presence of antibiotics to reduce bacterial growth[14].

Radiographic approaches to early diagnosis have become increasingly important. However, radiographic characteristics of pulmonary infection are variable and can include nodules or masses[15]. The physicians are encouraged to provide detailed clinical information to the radiologist to guide in diagnosis. In any post-transplant recipient patient persistent leucopenia, neutropenia and features of infection, fungal causes should be ruled out.

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Swyer syndrome, 46 XY gonadal dysgenesis: a case report

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ABSTRACT

The Swyer syndrome is one of the pure gonadal dysgenesis disorders with 46, XY Karyotype1. In this case study we discuss a 27-year-old female who presented with primary amenorrhoea and delayed puberty. The differential diagnoses included chromosomal irregularities, primary ovarian insufficiency, anatomic abnormalities and hypogonadotropichypogonadism. Diagnosis requires multi-disciplinary approach to provide multi-faceted care and induction of puberty and management of infertility. Genetic counselling and psychological support may be of benefit for affected individuals and their families.

Key words: Swyer, Syndrome, Gonadal, Chromosomal, Hypogonadism

INTRODUCTION

The Swyer syndrome is one of the pure gonadal dysgenesis disorders with 46, XY Karyotype[1]. The patients are by phenotype female with poorly developed uterus and fallopian tubes and have streak gonads. Most cases will have no mutations with about 15-30% of cases presenting with aberrations of chromosome Y or SRY gene mutation[1,2]. Patients present with primary amenorrhoea, delayed puberty as they do not produce any gonadal hormones. They have hypergonadotropic hypogonadism due to high gonadotropin levels[3]. They are predisposed to increased risk of neoplastic transformation in the dysgenetic gonads[4]. Bilateral gonadectomy is recommended once diagnosis is made[5]. Management involves induction of puberty with estrogen to develop secondary sexual characteristics and long-term combined replacement therapy with estrogen and progesterone[6]. Swyer syndrome is a rare condition that should be considered in females presenting with delayed puberty, primary amenorrhoea and high gonadotrophin levels. The incidence of Swyer syndrome is uncertain but is estimated at 1 in 80,000 births[1].

CASE REPORT

This is a case of a 27-year-old never married female who presented with primary amenorrhoea and delayed puberty. She developed pubic hair from the age of 13 years. She had no history of headache, visual disturbance, or cyclical abdominal pain. There was no family history of delayed puberty and was the only girl in a family of three children.

She had a height of 163 cm and on examination breast development was Tanner stage 2 bilaterally, no acne and no hirsutism noted. Acanthosis nigricans was present. She had normal female external genitalia with sparse axillary hair. Examination of the vagina showed patent vagina of 4cm. The differential diagnoses included chromosomal irregularities, primary ovarian insufficiency, anatomic abnormalities and hypogonadotropic hypogonadism.

Measurement of serum hormone levels, karyotyping and imaging studies were done and the results are shown in Table 1. Follicle-Stimulating Hormone (FSH) was elevated while estrogen and progesterone were low. The testosterone level was within the normal reference range for females. A peripheral blood karyotype study using the G-banding technique revealed 46, XY chromosomes, this male karyotype in a patient with female appearance suggested the diagnosis of Swyer syndrome. Pelvic ultrasound showed hypoplastic uterus and - gonads.

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Table 1: Results of diagnostic tests done

Serum hormones		
Parameter	Results	Reference interval
Follicle Stimulating Hormone:	85.77 mIU/mL	
Normal menstruating women		
Follicular phase:	1.4-9.9	
Mid cycle phase:	0.2-17.2	
Luteal phase:	1.1-9.2	
		Post-menopausal: 19.3-100.6
Estradiol	8.02pg/mL	
Follicular phase:	12.5-166	
Ovulating:	85.8-498	
Luteal phase:	43.8-211	
		Post-menopausal: 5-54.7
Progesterone	0.18 ng/mL	
Follicular phase:	0.2-1.5	
Ovulating:	0.8-3.0	
Luteal phase:	1.7-27	
		Post-menopausal: 0.1-0.8
Free testosterone	2.50 pg/mL 0.2-4.1	
Follicular phase:	0.45-3.17	
Luteal phase:	0.46-2.48	
Oral contraceptives:	0.55-2.01	
		Post-menopausal: 0.29-1.73
Karyotyping by G-Banding (Peripheral blood)	46XY	
Pelvic ultrasound:		
- Hypoplastic uterus/uterus agenesis		
- Hypoplastic gonads		

DISCUSSION

Most cases of Swyer syndrome are not inherited; they occur in people with no familial history, occurring either from non-genetic causes or from de no vo mutations in a gens during formation of reproductive cells or in early embryonic development[2,7]. SRY-related Swyer syndrome is usually caused by a new mutation. Some individuals inherit an altered SRY gene from an unaffected father who is mosaic for the mutation[7].

People with Swyer syndrome have typical female external genitalia as seen in this patient. The uterus and fallopian tubes are normally-formed, but the gonads (ovaries or testes) are not functional; affected individuals have undeveloped clumps of tissue called streak gonads. This patient had poorly developed gonads as reported above by ultrasound.

The diagnosis and management is complex and optimal care requires experienced multidisciplinary team. The diagnosis of Swyer syndrome is based on detailed patient history and physical examination, identification of characteristic findings like amenorrhoea with streak gonads and laboratory investigations including karyotyping. For this patient we were able to do hormonal profile, imaging and karyotyping.

The residual gonadal tissue often lead to increased risk of gonadal malignancies including gonadoblastoma and dysgerminomas. Due to increased risk for cancer early diagnosis and management is crucial. The preferred management is surgical removal at an early stage[4, 7].

Patients with Swyer syndrome may also present with other health conditions such as neuropathy which occurs as part of a syndrome such as campomelic dysplasia which causes severe skeletal abnormalities[8].

Affected individuals are usually began on hormone replacement therapy immediately during adolescence to induce menstruation and development of female secondary sex characteristics[5]. Hormone replacement therapy helps reduce the risk of osteopenia and osteoporosis due to lack of oestrogen[4]. Women with Swyer syndrome do not produce ova. However, pregnancy can be achieved with a donated egg or embryo[5,9]. A thorough evaluation to assess suitability for management should be done after which patients can be started on suitable medication including hormonal and

surgery treatment. Individuals with Swyer syndrome should undergo genetic counselling[9].

Differential diagnosis

Swyer's syndrome can be easily confused with mixed gonadal dysgenesis which is more common. In mixed gonodal dysgenesis the gonads on histopathology will also show both testicular and ovarian differentiation unlike for Swyer's syndrome.

Swyer syndrome is also indistinguishable from Complete Androgen Insensitivity Syndrome (CAIS). Patients with CAIS present with female phenotype and 46, XY karyotype. They present with primary amenorrhoea, with underdeveloped external female genitalia, better developed breasts, absence of pubic and axillary hair and uterus. They also have testis instead of ovaries with XY karyotype. CAIS presents in other family members so there is need to investigate other family members. Patients with CAIS are unresponsive to hormonal replacement therapy unlike patients with Swyer's syndrome.

Molecular studies

Swyer syndrome is due to several mutations including mutations in the DHH, MAP3K1 (18% of the cases), NR5A1 or SRY (15% of the cases). However, in most patients the cause is unknown. Therefore while diagnosis by molecular studies can help it is not helpful in the majority of the cases.

CONCLUSION

The diagnosis in this case was delayed and made at the age of 26 years. Early diagnosis of females presenting with amenorrhoea is important. Studies show that many women experience delays before definitive diagnosis is made hence medical practitioners should be aware of sexual development disorders. Due to the risk of developing tumours, extensive search for the rudimentary gonads is needed and bilateral gonadectomy is recommended. It thus requires multi-disciplinary approach to provide multi-faceted care in terms of prevention of malignancy and accompanying symptoms including osteoporosis and neuropathy, induction of puberty and management of infertility. Genetic counselling and psychological support may be of benefit for affected individuals and their families.

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