Malawi Medical Journal; 26(1): March 2014

Causes of cervical lymphadenopathy at Kamuzu Central Hospital

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Abstract

Aim

Description of pathologic causes of cervical lymphadenopathy at Kamuzu Central Hospital.

Introduction

The evaluation of cervical lymphadenopathy is a common diagnostic challenge facing clinicians. Previously at Kamuzu Central Hospital (KCH) tuberculosis (TB) was reported to be the most common cause of cervical lymphadenopathy However, no recent study has assessed this common diagnostic challenge in Malawi, particularly since the beginning of the HIV epidemic and the subsequent scale-up of antiretroviral therapy.

Methods

We conducted a cross-sectional study of all cervical lymph node specimens from the KCH pathology laboratory between 1 July 2011 and 28 February 2013 and describe patient age, gender, and pathologic diagnoses.

Results

Our search of the KCH pathology database yielded 179 cases. Of these, 143 (77%) were histologic specimens (open biopsy or core needle samples) while 34 (23%) were cytology specimens. The age range was from 0 to 76 years with a mean of 30 (SD: 19). In adults, the most common diagnosis was malignancy (n=41, 35%), while in children 15 cases each of malignancy and benign masses were diagnosed. Only 6 cases (5%) of TB were diagnosed in adults, and 4 cases (6%) of TB were diagnosed in children.

Conclusion

Our study shows more malignancy and much less TB than a prior study of cervical lymphadenopathy at KCH. With the successful initiaion of the KCH Pathology Laboratory in 2011, we recommend biopsy or FNA early in the workup of cervical lymphadenopathy to prevent long delays in diagnosis and treatment of curable cancers.

Introduction

Cervical lymphadenopathy is the commonest form of peripheral lymphadenopathy[1]. It has many causes, including benign, infectious and malignant conditions. The evaluation of cervical lymphadenopathy is a common diagnostic challenge facing clinicians. While a careful history and thorough physical exam can help identify the cause of lymphadenopathy, pathological examination is the definitive diagnostic test. Open biopsy is time consuming and costly, requiring theatre time and anesthesia. Fine needle aspiration (FNA) is less invasive, cheaper, and quicker. However, cytology from FNA specimens may have diagnostic limitations for many conditions compared with histologic evaluation of biopsy specimens. FNA analysis additionally requires a well-trained pathologist and is best done onsite, both rare commodities in many parts of sub-Saharan Africa[2]. Core needle biopsy is an intermediate technique in terms of cost, time, and information obtained, but can be dangerous in the neck, especially when performed by clinicians who are inadequately trained[3]. A clinician may also choose to empirically treat for tuberculosis (TB) or bacterial infection based on history and physical examination, and reserve biopsy or FNA for patients who do not respond to therapy. However, this strategy will delay definitive diagnosis and treatment of a malignancy. The optimal strategy for evaluating cervical lymphadenopathy in resource-limited settings like Malawi is largely unknown given the relative advantages and disadvantages of these varying approaches, particularly in light of recent expansion of diagnostic pathology services to Lilongwe.

A large body of literature suggests that TB is the most common cause of cervical lymphadenopathy in sub-Saharan Africa, accounting for 17-66% of cases[1, 4, 6-23]. In Malawi, at Kamuzu Central Hospital (KCH) during the years 1985-1988, TB was reported to be most common cause lymphadenopathy[4]. However, no recent study has assessed causes of cervical lymphadenopathy in Malawi in the modern era, particularly since the beginning of the HIV epidemic and rapid scale-up of antiretroviral therapy (ART) nationwide among HIV-infected individuals. Currently, more than 60% of those needing ART are now receiving it[5]. In this study, we describe the pathological diagnoses for patients with cervicallymphadenopathy presenting to KCH who underwent a diagnostic biopsy. We also suggest strategies to improve diagnosis and management of patients with cervical lymphadenopathy.

Methods

Laboratory diagnostic procedures

The KCH Pathology Laboratory became operational in July 2011 with Professor George Liomba now reviewing specimens and providing laboratory direction. Two histology and cytology technicians underwent training in South Africa and have returned to staff the laboratory. The lab currently accepts specimens from KCH outpatient clinics, inpatient wards and operating rooms. During the period reported in this paper, diagnoses were based on morphology without the assistance of immunohistochemistry (IHC), flow cytometry, or molecular diagnostic tools. IHC methods, however, are now being introduced. Operating procedures, as well as quality assessment and control systems have been clearly established, and include regular review by UNC pathologists to insure diagnostic accuracy during weekly real-time telepathology conferences using the virtual microscopy system.

Data sources and analysis

At the time of specimen collection and submission to the laboratory, requesting clinicians complete a standardised pathology requisition form, including patient demographics (age, gender, HIV status, antiretroviral therapy status), brief clinical information, and specimen details (including site of biopsy, type of specimen, and date of collection). The laboratory then assigns each specimen a unique laboratory number, and enters details from the requisition form as well as specimen information and the pathologist's conclusions into a secure KCH pathology database. Longitudinal data regarding clinical course and treatment is not available.

Review of the database was approved by the Malawi

National Heath Services Committee(protocol ##1124) and the UNC Internal Review Board (UNC IRB # #13-0047). We conducted a retrospective cross-sectional study of all cervical lymph node specimens from the KCH pathology laboratory between 1 July 2011 and 28 February 2013. Salivary glands (submandibular and sublingual) biopsies were also included, as they often contain nodal tissue. Mandible, facial and thyroid masses were excluded. Diagnoses were categorized as non-diagnostic, malignant, tuberculosis, non-tuberculous infection, reactive adenopathy, benign mass (i.e., pleomorphic adenoma, lipoma, pyogenic granuloma), normal tissue, or other process. According to usual local practice, tuberculosis was diagnosed typically based on cha acteristic necrotizing granulomatous inflammation, without the demonstration of mycobacteria by smear or culture in most cases. Data were entered into Microsoft excel spreadsheets and Stata 12 (StatCorp, College Station, Texas, USA) was used for all analyses. Descriptive statistics were used to measure numbers of specimens assessed, specimen types, and final diagnoses. Differences in proportions and means between patients with non-diagnostic specimens were analyzed using chi-square. Pediatric cases were analyzed separately, defined as patients less than 16 years.

Results

Our sample size was 179 as defined by all biopsies sampled from the cervical lymph nodes. search of the KCH pathology database yielded a total of 179 cases of cervical adenopathy. Of these, 143 (77%) were histologic specimens (open biopsy or core needle samples) while 34 (23%) were cytology specimens. The age range was from 0 to 76 years with a mean of 30 (SD: 19). Adults (16 years of age or older) accounted for 121 (68%) of the study population with a mean age of 40 (SD: 15). Women accounted for 65 (54%) of adult cases. The mean age among pediatric cases was 8 years (SD: 5, n=58). Of the 58 paediatric cases, 35 (60%) were female (Table 1).

Table 1: Characteristics of Neck Node Biopsy Patients (n=179) at KCH from July 2011 to February 2013

CHARACTERISTIC	MEAN or N*	SD or %
Pediatric patients (< 16 years)	58	33%
Age (years)	8.1	5.1%
Male	22	38.6%
Female	35	61.4%
Adult patients (16+ years)	118	67%
Age (years)	40.4	14.4%
Male	53	44.9%
Female	65	55.1%

** Gender is missing for one pediatric case, and age is missing in three cases, therefore percentages are based on totals excluding missing patients. KCH- Kamuzu Central Hospital*

The most common diagnosis in adults was malignancy (n=41, 35%), followed by benign mass (n=25, 21%), non-TB infection (n=17, 14%), non-diagnostic cases (n=13, 11%), reactive adenopathy and normal tissue (n=7, 6%) each. TB accounted for 6 (5%) of cases (Table 2). Of the 41 adult malignancies cases, 11 (27%) were non-Hodgkin's lymphoma (NHL), 10 (24%) were squamous cell carcinoma (SCC). Four (10%) were nasopharyngeal carcinoma (NPC), 4 sarcoma (excluding KS), and 1 (2%) Hodgkin's lymphoma. A third of the biopsies (n = 58) were from children. (Table 1). Among children, malignancy and benign masses were the most common, with 15 cases (26%) each (Table 2).

Table 2 Frequency of Histopathological Diagnosis in Lymph Node Biopsies at KCH from July 2011 to February 2013

DIAGNOSIS	N	%
Pediatric patients (<16 years)	58	
Malignant	15	25.9%
Benign Mass	15	25.9%
Non-diagnostic	7	12.1%
Non-tuberculous infection	5	8.6%
Reactive adenopathy	5	8.6%
Normal Tissue	5	8.6%
TB	4	6.9%
Other process	2	3.5%
Adult Patients (16+ years)	**118**	
Malignant	41	34.8%
Benign mass	25	21.2%
Non-tuberculous infection	17	14.4%
Non-diagnostic	13	11.0%
Reactive adenopathy	7	5.9%
Normal tissue	7	5.9%
TB	6	5.1%
Other process	2	1.7%
Total	**176**	

** Age is missing in three cases, therefore percentages are based on totals excluding missing patients.*

Non-diagnostic specimens accounted for 7 cases (12% Non-tuberculous infection, reactive nodes, and normal tissue each accounted for 5 cases (9%). TB was diagnosed in 4 cases (7%). Of the 15 pediatric malignancies, Hodgkin's lymphoma was the commonest with 6 cases (40%), followed by unspecified lymphoma 4 cases (27%). There was a single case of non-Hodgkin's lymphoma (Table 3).

Of the 21 non-diagnostic cases, 14 (67%) were from FNA specimens and 7 (33%) were from histology specimens. In total, one-third of all FNA specimens were inadequate for diagnosis, while only 9 (6%) histologic specimens were non-diagnostic. FNA specimens had a 9.3 times greater odds of being inadequate than histology specimens (95% CI: 3.4-25.1, $p<0.001$).

Table 3 Malignancies Diagnosed in Lymph Node Biopsies in Adult and Pediatric Patients at KCH from July2011 to February 2013

Diagnosis	N	%
Adults (>15 yrs)		
Non-Hodgkin lymphoma	11	27
Squamous cell carcinoma	10	24
Sarcoma*	4	10
Nasopharyngeal carcinoma	4	10
Carcinoma NOS‡	3	7
Kaposi sarcoma	2	5
Small round blue cell tumor NOS	2	5
Lymphoma NOS‡	2	5
Salivary gland carcinoma	2	5
Hodgkin lymphoma	1	2
Total	**41**	**100**
Children (<16 yrs)		
Hodgkin lymphoma	6	40
Lymphoma NOS‡	4	27
Nasopharyngeal carcinoma	2	13
NOS‡	2	13
Non-Hodgkin lymphoma	1	7
Total	**15**	**100**

**Excluding Kaposi sarcoma*

‡ Not otherwise specified

Discussion

The pathologic diagnosis of biopsied cervical lymphnodes at KCH has changed markedly over the past 20 years, and differ significantly from patterns reported in other sub-Saharan countries. In our population, we found more malignancy and little TB . In our population, less than 10% of adults or children with a pathologically confirmed cause of cervical lymphadenopathy were diagnosed with TB. TB prevalence and mortality have declined in Malawi over the past two decades, and prevalence in Malawi (164/100,000) is significantly lower than neighboring Mozambique (490/100,000) and Zambia (352/100,000)[24]. While reported TB cases have modestly declined over the past two decades, we identified seven times fewer cases of TB in cervical lymph node biopsies at KCH than a study at the same institution 25 years ago[4]. In Malawi, over 5,000 cases of extrapulmonary TB were diagnosed in 2011 alone[24]. While the apparent decline in TB as a cause of cervical lymphadenopathy at KCH in our study may reflect a changing disease burden in Malawi, it may also reflect selection and referral bias, given that patients who respond to empiric TB treatment may not undergo FNA or biopsy for cervical lymphadenopathy. In our study, malignancy is also more common than described in the previous KCH study[4]. We found that one in three cervical lymph nodes that were biopsied were malignant. The high proportion of patients with cancer in our sample likely reflects selection and referral bias as noted above, but also increasing cancer incidence overall in Malawi[25]. Among all cancer, lymphoma was the most common in both adult and pediatric patients. Interestingly, we identified few cases of Burkitt lymphoma, even though this disease is common in the region. Because Burkitt lymphoma commonly presents as facial or abdominal masses, which were excluded from our study, these patients would have been underrepresented in our cervicallymphadenopathy series. Squamous cell carcinoma (SCC) of the head and neck was found in 10% of the adult population referred for biopsy. This represents cervical nodal metastasis of a likely upper aerodigestive tract primary. Cervical nodal SCC should prompt a search for the primary site in the oral cavity, oropharynx, larynx hypopharyx or lung. Cliniciansshould be aware that airway obstruction is common in these patients. The high frequency of cancer diagnoses in our study suggests a need for rapid evaluation and pathologic diagnosis for unexplained cervical lymphadenopathy at KCH, such that potentially curative treatment can be provided to patients before they progress to more advanced stages of cancer which may be less amenable to cure. More than one in ten samples included in our study was non-diagnostic. Non-diagnostic samples translate to longer waiting times for both clinicians and patients before obtaining a definitive diagnosis and initiating treatment. FNA specimens had greater odds of being inadequate for diagnosis, which is consistent with previous studies[6]. Previous research suggests that experienced clinicians who perform FNA frequently have greater diagnostic yield from FNA specimens[26]. We can improve the work-up and management of neck nodes in our setting by biopsying patients early in the work up of cervical lymphadenopathy, improving training in biopsy techniques, improving clinical data collection on pathology forms, and expanding provision of pathology services to include samples from district hospitals. Since July 2011, pathology results have often been available within 72 hours; however, treating TB empirically remains the norm in referring clinics. This practice could will lead tocause a delay in diagnosis of cancer, and anedoctally we have seen many patients at KCH with clearly malignant masses which have been progressing on inappropriate TB treatment for many months before being referred. We hope that as pathology services become more available, clinicians will move away from empirical treatment of TB for cervical lymphadenopathy. Clinicians are greatly encouraged to insist on a confirmed pathologic diagnosis wherever possible to avoid delays in appropriate treatment. KCH is already working towards improving yield from FNA, and has conducted training for doctors and clinicians, as well as implementing an FNA clinic staffed by Prof. Liomba, which will help reduce the number of non-diagnostic cases. Preparation of cell blocks from FNA specimens which can undergo IHC staining is also being implemented and will increase the diagnostic yield. Clinicians are encouraged to work closely with the pathology laboratory to improve specimen preparation and to avoid common mistakes that impede timely diagnosis. Delineating clinical features of benign versus malignant cervical lymph nodes in our population could help prevent unnecessary biopsies of harmless lesions, and more importantly, prevent long delays in diagnosis and treatment of curable cancers. Clinicians are greatly encouraged to fully complete request forms including clinical history and HIV status, to provide robust data for ongoing research efforts to define optimal diagnostic

algorithms. Our study is limited by incomplete clinical information on pathology requisition forms submitted to the laboratory. HIV status was infrequently recorded, such that less than one in seven cases in our study known HIV status. Furthermore, clinical information was often sparse, which may hinder the pathologist's diagnosis of the individual specimen. These limitations are common in retrospective studies like ours, particularly in sub-Saharan Africa where clinical data systems are often weak. Additionally, our data are drawn froma national referral hospital. Patients with cervical lymphadenopathy are often seen first at local health clinics, then referred to district hospitals, and finally sent to KCH months later. Our data probably do not fully represent patients with aggressive malignancy who died before presentation to KCH, or patients whose adenopathy resolved with TB treatment or antibiotics.

In conclusion, our study shows more malignancy and less TB than a previous KCH study of cervical lymphadenopathy. Continued research efforts should include a prospective study of cervical lymphadenopathy, enrolling patients directly from clinic to minimize biases discussed above. As turn-around time for biopsy specimens at KCH continues to improve, we recommend performing biopsy or FNA early in the workup of cervical lymphadenopathy to prevent long delays in diagnosis and treatment of various medical conditions, including potentially curable cancers.

Acknowledgements

Claire Kendig and Satish Gobal are supported by the National Institutes of Health Office of the Director, FogartyInternational Center (1R25TW009340-01). Satish Gopal is also supported by an International ResearchScientist Development Award from the NIH Fogarty International Center (1K01TW009488-01). This work was alsosupported by the University of North Carolina Center for AIDS Research, an NIH-funded program (P30 AI50410).

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