Diagnosing lymphoma in the shadow of an epidemic: lessons learned from the diagnostic challenges posed by the dual tuberculosis and HIV epidemics

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Abstract

Infectious disease epidemics may overshadow and exacerbate existing challenges in diagnosing lymphoma. We describe pragmatic strategies we have implemented to overcome diagnostic obstacles caused by the local tuberculosis (TB) and HIV epidemics in South Africa, which may serve as a guide to minimise diagnostic delay during the COVID-19 pandemic. We report on the diagnostic utility of a rapid-access lymph node core-biopsy clinic, where lymph node biopsies are taken from outpatients at their first visit. Analysis of tissue biopsies (n=110) revealed the three most common conditions diagnosed were TB adenitis (34%), lymphoma (29%), and disseminated malignancy (20%). A first-attempt core-biopsy was able to diagnose lymphoma in 27/32 (84%) of cases. Compared with a historical cohort, the *diagnostic interval* (time from first health visit to diagnostic biopsy) for patients with lymphoma was significantly shorter, 13.5 vs 48 days (p=0.002).

Keywords

lymphoma; COVID-19; HIV; diagnosis; tuberculosis

Introduction

South Africa has been at the epicentre of the colossal dual HIV and tuberculosis (TB) epidemics which have posed several challenges in the diagnosis of lymphoma. Globally, we are now facing a new infectious disease epidemic. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease (COVID-19) has infiltrated every aspect of daily life. As of the 8th of June 2020, over 7 million cases have been confirmed

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worldwide, with over 400,000 deaths. The burden placed on healthcare resources, as well as measures taken to reduce transmission risk of SARS-CoV-2 are likely to intensify the existing challenges in the diagnosis of lymphoma. We describe measures we have implemented to enhance the diagnosis of lymphoma under the menacing shadow the dual infectious disease epidemics which could be applied during the COVID-19 pandemic.

Before the COVID-19 pandemic, difficulties and delays in lymphoma diagnosis had already been highlighted in several papers from developed countries[1,2]. Our report on the diagnostic pathway of lymphoma in the developing world has confirmed that these delays are predominantly during the *diagnostic interval* (first healthcare visit to diagnosis), and to a lesser degree within the *patient interval* (symptom onset to help-seeking)[3]. A delay in diagnosis was found to be associated with late-stage disease[3], which is associated with poorer outcomes. Even in the most well-resourced healthcare settings, patients frequently have a string of general practitioner (GP) visits before being referred to hospital[2]. Numerous barriers to diagnosis have been identified, including lack of symptom specificity, lack of a distinct referral pathway for lymphadenopathy, and difficulties in obtaining sufficient tissue for diagnosis, particularly as the fine-needle aspirate (FNA) for cytology has a low diagnostic yield for lymphoma[4]. In TB endemic settings lymphoma diagnosis is further complicated by overlapping symptoms with extrapulmonary TB and lymphoma may frequently be misdiagnosed as TB[5,6].

Transmission risk during the COVID-19 pandemic has been mitigated by using teleconsultations, reducing in-person consultations, restricting elective procedures and phlebotomy[7]. These strategies may interfere with detection of lymphoma both during the *patient interval* and the *diagnostic interval*. Patients with slow-onset and gradually progressive symptoms are more likely to wait longer before seeing their GP. Important clinical findings, such as pallor, lymphadenopathy, or splenomegaly, may be missed in a teleconsultation. And finally, because elective surgeries have been reduced or cancelled as a result of the pandemic, fewer excisional lymph node biopsies can be performed. This has recently been highlighted in a paper showing a 57% reduction in patients being referred to a specialist haematologist and a 49% decrease in lymphoma diagnosis in the United Kingdom[8].

Recognising the significant hurdles to lymphoma diagnosis, we set up a dedicated rapid-access lymph node biopsy clinic and a diagnostic awareness campaign aimed at doctors starting in 2017. The diagnostic outcomes of the first 99 patients from this patient group have been reported, with a focus on the diagnostic utility of the MTB/Rif Gene Xpert Ultra (Ultra) for the diagnosis of TB adenitis[9]. Here we describe how the clinic has facilitated more rapid lymphoma diagnosis and report on the accuracy of the core core-biopsy method for the diagnosis of lymphoma.

Methods

We established a rapid-access lymph node biopsy clinic in November 2017. The clinic is run from the Division of Clinical Haematology at the University of Cape Town and Groote Schuur Hospital, a tertiary referral academic centre in Cape Town, South Africa. Eligible

study participants were adults (18 years), both in- and outpatients, and referred with enlarged lymph nodes of > 20 mm diameter in either the cervical, axillary, or inguinal region. Patients with contraindications to core-biopsy (low platelets, other coagulopathy, clinically unstable, or unsafe biopsy site) were excluded. Written informed consent was obtained from all participants. The Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town, approved the study.

Patients were referred to Groote Schuur Hospital from secondary level hospitals and day clinics in the referral area. We implemented a regional educational outreach to these centres to raise awareness of lymphoma as a common alternate diagnosis to TB and HIV and to highlight the importance of adequate tissue sampling for lymphoma detection. Referrals were made to the clinic using an electronic method in the form of a short survey that could be filled in on a mobile phone, which provided patient demographic and clinical data on a secure data platform. Patients were seen within 7 days of referral.

Because of the TB endemic, fine-needle aspiration (using a 22-G needle and 5 ml syringe) was performed first to check for caseous material; if > 0.5 ml of caseous material was aspirated, the MTB/Rif Xpert Ultra assay, air-dried smear for acid-fast bacilli (AFB) using the Ziehl–Neelsen stain and a TB culture were performed(9). The methods for TB culture and Ultra are described elsewhere(9). A biopsy was not performed if the enlarged mass was in a submandibular gland; in this case, FNA for cytology was performed. In all other cases, a core-biopsy was performed using an automated biopsy gun (BARD MagnumTM, CR Bard Inc., Covington, GA, USA) with a 14-G needle in the haematology clinic. If the lymph node was not easily palpable, the biopsy was performed under handheld ultrasound guidance. Two or three cores were put in formalin for histology (10–15 mm long), and one core was cut in two and sent for TB culture and Ultra in 2 ml of 0.9% saline. If all test results were inconclusive, the patient underwent either a repeat core-biopsy or an excision biopsy at the discretion of the treating clinician.

Histological review was performed by an anatomical pathologist. Participants were diagnosed with TB adenitis if the culture or Ultra was positive, or if AFBs were identified on the smear or tissue(10). Lymphoma was diagnosed according to the 2016 WHO classification of lymphoid neoplasms[10].

We compared time-to-diagnosis for patients with lymphoma with a historical lymphoma cohort treated at the same tertiary institution(3). The time to diagnosis was described in the following time intervals: *patient interval* (self-reported symptom onset to first healthcare provider consultation) and *diagnostic interval* (first healthcare contact to a diagnostic biopsy). We also report the *referral interval* (time from the completion of the referral survey to a diagnostic biopsy) as a measure of clinic efficiency, we could not compare this to a historical cohort.

Data were entered into a REDCap® database and analysed using the STATAv14 software package (StataCorp, College Station, Texas, USA). Baseline clinical characteristics were compared using the chi-squared or Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables.

Results

Between November 2017 and August 2019, 130 consecutive patients underwent investigations for lymphadenopathy; 46% were male with a median age of 36 years (interquartile range 30–50 years). The majority of patients were seen as outpatients (84%) and had a good performance status (Table 1). Sixty-four patients (49%) were HIV positive, with a median CD4 count of 274 cells/mm^3 and 20 (31%) were virally suppressed (viral load less than 40 copies/mL); 42 patients (65%) were on antiretroviral therapy.

FNA alone was performed in 20 patients and revealed a diagnosis of TB adenitis in 14 (70%) of these patients (Table 1). In the remaining 110 patients, a core-biopsy was performed. In 98 (89%) patients, a diagnosis was made on the first core-biopsy, while the remaining 12 patients required a second biopsy (six excision biopsies and six repeat core-biopsies). The final diagnoses from both FNA and core-biopsy procedures are presented in Table 1.

Thirty-two patients were diagnosed with lymphoma, 30 of whom (94%) were diagnosed from core-biopsies and 27/32 (84%) were diagnosed from the *first-attempt* core-biopsy. Of the 30 cases of lymphoma diagnosed from a core-biopsy, 27 were subtyped and most were found to be diffuse large B-cell lymphomas and Hodgkin lymphomas (Table 2). Histological features of core-biopsies in three patients were suggestive of lymphoma, but a definitive diagnosis could not be made: plasmablastic lymphoma *or* Castleman's disease (the patient died before an excision biopsy could be performed); 'atypical lymphoid proliferation' (the patient declined excision biopsy); and Hodgkin lymphoma *or* anaplastic large-cell lymphoma (the patient could not be contacted for a repeat biopsy).

In 7/32 (22%) lymphoma cases, the referring clinician had indicated that they suspected TB adenitis to be the most likely cause, and TB treatment had been started presumptively (in all of these patients Xpert MTB/Rif assay was negative on sputum), and in four cases the chest radiograph was considered compatible with TB by the referring doctor (hilar adenopathy [n=1], pleural effusion [n=1], parenchymal disease [n=2]).

The *patient-interval* for patients with lymphoma was a median of 42 days (IQR 23-92 days), compared with a median of 25 days (IQR 9.5-61) from the historical cohort of lymphoma patients, p=0.01. The *diagnostic interval* was a median of 13.5 days (IQR 8.5-53.5 days); compared with a median of 48 days (IQR 21-116) for the historical cohort, p=0.002. The median *referral interval* was 3 days (IQR 2-8).

Discussion

We report an online referral system and accurate diagnostic procedure in a rapid-access lymph node biopsy clinic. The measures we have implemented have significantly reduced the time to lymphoma diagnosis. These three key measures are: 1. educational outreach coupled with access to a convenient e-method for referring doctors, overcoming local barriers between peripheral need and centralised expertise; 2. a rapid biopsy technique with a high diagnostic yield for lymphoma which can be performed at the bedside by a healthcare practitioner without specialist surgical or radiological training; and 3. a change in referral

criteria to the haematology service from proven lymphoma to the evaluation of suspected lymphoma or lymphadenopathy of unknown aetiology.

While very different to acute illnesses like COVID-19, we face significant challenges posed by the overshadowing of cancer by the dual epidemics of TB and HIV, which together account for 150,000 deaths annually in South Africa(11,12). Infectious disease epidemics may create a clinical diagnostic bias towards conditions frequently associated with these epidemics(3). In HIV/TB-endemic areas lymphoma may be delayed or missed due to overlapping clinical features with TB e.g. lymphadenopathy and B symptoms and similar investigation findings (cytopenias, granulomas on cytology, pleural effusions, hypodense splenic lesions, and tree-in-bud infiltrations on computerised chest tomography scan)(13). Misdiagnosis of lymphoma as TB has been highlighted in several studies, showing that in TB endemic areas, up to 85% of patients with lymphoma may be initially misdiagnosed as TB(5,14).

Conventionally, excision biopsy has been preferred over FNA or core-biopsy as the method of choice for tissue acquisition from patients with lymphadenopathy because the nodal architecture can be evaluated, and sufficient tissue can be collected for immunohistochemical stains and molecular tests. However, theatre time and surgical expertise can be significant barriers to obtaining an excision biopsy. Core-biopsy has been proposed as a reasonable first diagnostic procedure for lymphoma(15), as well as in patients with lymphadenopathy and HIV(16). The automated device extracts a cylinder of tissue and is preferred because the speed of the cutting mechanism provides a clean edge with fewer shearing artefacts(15). The core-biopsy method described in this paper accurately diagnosed 94% of lymphoma cases, and it can be performed as an outpatient or ambulatory procedure under local anaesthetic.

Compared with the historical cohort of patients at our institution with lymphoma, the *patient-interval* reported in this study was longer. This measurement may be inaccurate due to recall bias or chance as we would not have expected our clinic or methods to have an impact on the *patient interval*. Measures that may shorten this interval during the COVID-19 pandemic include public health messages about the significance of lymphadenopathy, and measures taken by the doctor's rooms to alleviate patient anxiety about transmission risk. The *diagnostic interval* was significantly shorter due to the implementation of the clinic and biopsy methods (median 25 days compared with 42 days). The *referral interval* was particularly short, at a median of only three days from referring a patient to obtaining a biopsy. Both of these represent an important and significant improvement in the time-to-diagnosis of lymphoma.

An overarching and core theme in the implementation of this clinic is the change in referral criteria to the Haematology service, from proven lymphoma to suspected lymphoma. This demonstrates concern and interest by the Haematologist to intervene on measures upstream from diagnosis has included the training of Haematology registrars to perform the lymph node biopsies. In addition to providing access to a biopsy, within the hospital setting haematologists are more likely to have access to other diagnostic services such as specialised imaging, bone marrow biopsy and flow cytometry. It also enables an expert, with an

understanding of the indications and limitations of investigations, to guide the diagnostic process. Ultimately, this change shifts the diagnostic burden away from the primary care physician and toward the Haematologist. During the COVID-pandemic, as access to primary care visits are limited, this shift in diagnostic responsibility may help identify patients who require investigations expediently and decrease the risk of a delay in the diagnosis of lymphoma.

Conclusion

The dual HIV/TB epidemic has created challenges in the diagnosis of lymphoma in our setting. The COVID-19 pandemic presents a new challenge to the haematology community and the issues that arise will require thought and engagement as we advocate for improvement in diagnostic services for patients with lymphoma. The focused measures we have applied in our rapid-access lymph node biopsy clinic have decreased the diagnostic interval in a TB/HIV endemic setting and may improve lymphoma diagnosis during the challenging COVID-19 era and beyond.

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Table 1.

Patient information and diagnosis

Male	60 (46%)
HIV positive	64 (49%)
Performance score *	
ECOG 0	61 (47%)
ECOG 1	40 (31%)
ECOG 2	8 (6%)
ECOG 3	18 (14%)
ECOG 4	3 (2%)
Patient type	
Inpatient	21 (16%)
Outpatient	109 (84%)
Site of biopsy	
Neck	95 (86%)
Axilla	10 (9%)
Inguinal	5 (4%)
Diagnosis	
FNA only (n=20)	
TB adenitis	14 (70%)
Bacterial adenitis	2 (10%)
Submandibular salivary gland	4 (20%)
Core-biopsy (n=110)	
TB adenitis	37 (34%)
Lymphoma	32 (29%)
Other malignancy	22 (20%)
Reactive lymph node	8 (7%)
Sarcoidosis	2 (2%)
Bacterial adenitis	3 (3%)
Other **	6 (5%)

**
Other (not a lymph node(3) Sinus histiocytosis (1), granulomatous unknown(1), previous TB with scarring(1))

*
ECOG=Eastern Cooperative Oncology group(16); HIV=human immunodeficiency virus; FNA= fine-needle aspirate; TB=tuberculosis

Table 2.

Lymphoma type and subtype

Diffuse large B-cell lymphoma (n=13)	
Activated B-cell	5
Germinal centre *	5
EBV-associated	1
HHV-8-associated	1
Unable to subtype	1
Hodgkin lymphoma (n=14)	
Nodular-lymphocyte predominant	2
Classical	
Nodular sclerosing	3
Mixed cellularity	1
Lymphocyte rich	1
Unable to subtype	7
Follicular lymphoma	1
Burkitt lymphoma	1
Lymphoma unclassified	3

*
excision biopsy in two of the germinal centre cases

EBV=Epstein–Barr virus; HHV-8 = human herpes virus-8