Int J Clin Exp Pathol 2019;12(8):3102-3107
www.ijcep.com /ISSN:1936-2625/IJCEP0096746

Original Article

The causes of lymphadenopathy in the central region of Saudi Arabia: a clinicopathological analysis of 475 cases

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Received May 9, 2019; Accepted May 27, 2019; Epub August 1, 2019; Published August 15, 2019

Abstract: Lymphadenopathy (LAP) is a common working diagnosis in the primary care setting; although the underlying etiology of this condition can be self-limiting, serious causes need to be ruled out. A clear understanding of lymph node (LN) location and patient demographics and exposure is vital in identifying which cases require rapid and extensive workup. The incidence of tuberculous (TB) lymphadenitis in the Central Region of Saudi Arabia (CRSA) has been reported to be 37.8%. In this study, we aimed to investigate the causes of LAP in this region. This was a retrospective study evaluating all patients who underwent LN biopsy at King Abdulaziz Medical City, Riyadh between 2007 and 2017. A total of 475 patients met the eligibility criteria. The mean age was 40.9 ± 25.5 years; 203 (42.7%) were females and 447 (94.1%) were Saudis. The causes of LAP were malignant in 240 (50.5%) and benign in 235 cases (49.4%). Forty two (8.8%) cases had TB lymphadenitis, but only 17 (40.5%) of those presented with systemic symptoms. Malignant causes were more common in adults compared to children, at 209 cases (55.4%) and 31 cases (31.6%), respectively (P = 0.0001). Patients who presented with generalized LAP were more likely to have a malignancy (P = 0.0000). Of the 234 who presented with systemic symptoms, 138 (59%) were diagnosed with cancer (P = 0.0000). Although less prevalent than before, TB lymphadenitis remains a significant medical problem in the CRSA. Malignancy must be ruled out, especially in those who present with generalized LAP and those with associated systemic symptoms.

Keywords: Lymphadenopathy, lymph node biopsy, tuberculous lymphadenitis, malignancy, Saudi Arabia

Introduction

Lymphadenopathy (LAP) is a common presentation in the primary health setting. Although the etiology of this condition is mostly benign in the pediatric age group, careful examination and follow up are essential to exclude malignancy [1, 2]. The underlying etiology can be self-limiting in adults; however, serious causes are more common and must be ruled out [3]. Cervical LAP is most commonly due to infections; however, supraclavicular involvement, a LN size more than three centimeters, and/or a duration more than four weeks with an abnormality in the laboratory results may indicate the presence of malignancy [1, 2]. A clear understanding of the lymph node location, description, along with patient demographics and exposure, is vital in identifying which cases of LAP require rapid and extensive workup compared to those that can simply be observed [4, 5].

In developing countries, mycobacterial tuberculosis (TB) is the most common benign etiology for LAP, especially in patients presenting with cervical LAP [6-9]. In developed countries, TB lymphadenitis is usually a disease associated with immigrants, those born in foreign countries or those with human immunodeficiency virus (HIV) [10, 11]. Despite significant efforts to control TB infection in Saudi Arabia, this disease remains a significant public health problem in different regions of the Kingdom, affecting all age groups [12]. According to the 2018 World Health Organization (WHO) global report,

Table 1. Patient characteristics

	N (%)
Age mean years (standard deviation)	40.9 (25.5)
Age group	
Adult	377 (79.4)
Pediatric	98 (20.6)
Gender	
Male	272 (57.3)
Female	203 (42.7)
Nationality	
Saudi	447 (94.1)
Non-Saudi	28 (5.9)
Total	475 (100%)

the incidence of TB in Saudi Arabia is 10 per 100000 of the population range (8.6-12) [13]. In the central region (Riyadh), the rate of TB infection ranges from 8.5% to 22% but is as high as 23.1% in the northern region (Hail), and up to 22-38% in the western region (Jeddah and Makkah) [14, 15].

In this study, we aimed to investigate the causes of LAP in the central region of Saudi Arabia with particular emphasis on TB lymphadenitis.

Methodology

The Ministry of National Guards Health Affairs (MNGHA) provides medical care for National Guards employees and their dependents. King Abdulaziz Medical City (KAMC-MNGHA) is the MNGHA medical center in the capital city Riyadh; this is a 1200 bed tertiary referral center that also accepts other locals with suspected or confirmed serious diagnoses, such as cancer. In this retrospective study, and with ethical approval from the King Abdullah International Medical Research Center, we retrospectively identified all patients who underwent lymph node (LN) biopsy at KAMC-MNGHA between 2007 and 2017. As there was no interaction with patients, and no need for new tissue biopsies, informed consent was waived. We included all patients who presented with LAP as a primary working diagnosis and patients in whom LAP was an incidental finding during evaluation for other medical problems. We excluded all patients with a known history of malignancy over the past five years, and those who had LN biopsy as part of cancer staging. If a patient underwent more than one LN biopsy at different times, then the subsequent biopsies were excluded.

We extracted clinical data from medical records, including patient demographics and their presenting signs and symptoms. We also determined the type of biopsy: excisional, true cut/open, core or fine needle aspiration and biopsy (FNA). In addition, we reviewed the clinical and radiological data to determine the extent of LAP.

All lymph node pathology slides were analyzed by pathologists employed by KAMC-MNGHA and mostly read by one of the coauthors (SA). The WHO Classification for malignancies was used as a reference for diagnosis. The diagnosis of TB lymphadenitis was made using the Ziehl-Neelson stain for acid fast bacilli and was confirmed by mycobacterium tissue culture.

Data were entered into a Microsoft Access database and were reviewed for consistency and validity. The data were then exported to IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY, USA) for analysis. Frequencies of nominal categorical variables were compared by the Chi-square test, and continuous variables were compared by t-tests. P values < 0.05 were considered statistically significant.

Results

Of the 617 lymph node biopsies performed between 2007 and 2017, 142 were excluded because they were performed as part of a staging process or confirmation of disease relapse in patients with known cancer. Among the remaining 475 eligible patients, the mean age was 40.9 ± 25.5 years; 377 (79.4%) were adult patients (15 years of age or older) and 272 (57.3%) were males. Patient characteristics are shown in **Table 1**. The types of biopsies performed were excisional in 219 cases (46.1%), needle core in 229 cases (48.2%), true cut/open biopsy in 25 patients (5.3%) and fine needle aspiration and biopsy (FNA) in two cases (0.4%).

The cause of LAP was malignant in 240 cases (50.5%) and benign in 235 cases (49.5%). Among the benign causes, reactive/non-specific lymphadenitis was the most common in 137 patients (58.3%), followed by TB lymphadenitis

Table 2. Pathological diagnoses

Pathological diagnosis	N (%)
Reactive/non-specific lymphadenitis	137 (28.8)
Non-Hodgkin lymphoma	114 (24.0)
Hodgkin lymphoma	102 (21.5)
Tuberculosis lymphadenitis (non-necrotizing granulomatosis)	42 (8.8)
Solid tumors	17 (3.6)
Necrotizing granulomatosis	18 (3.8)
Other hematological malignancy	7 (1.5)
Kikuchi-Fujimoto disease	6 (1.3)
BCG lymphadenitis	6 (1.3)
Langerhans histocystosis	5 (1.1)
Sarcoidosis	4 (0.8)
Castleman disease	3 (0.6)
Brucellosis	3 (0.6)
Others	11 (2.3)

'Others': Dermatopathic lymphadenitis, neurofibroma, Kimura disease, cortical hyperplasia secondary to systemic lupus erythematosus (SLE) or rheumatoid arthritis, Human Immune deficiency virus (HIV) lymphadenitis.

(non-necrotizing granulomatosis) in 42 patients (17.9% of all benign causes; 8.8% of the entire cohort). Among the patients diagnosed with TB lymphadenitis, only 20 cases (47.6%) presented with cervical LAP, six (14.3%) with mediastinal, four (9.5%) with axillary LAP and only 17 (40.5%) presented with constitutional symptoms such as fever, nocturnal diaphoresis and weight loss.

Malignant causes were mostly hematological 225 cases (92.9%): 114 (47.5%) with non-Hodgkin lymphoma, 102 (42.5%) with Hodgkin lymphoma and seven (2.9%) with other hematological malignancies. Solid tumors were only diagnosed in 17 patients (7.1%). The pathological diagnoses are given in **Table 2**. Malignant causes were more common in adults than in pediatrics (209 (55.4%) *vs.* 31 (31.3%)) (P = 0.0001). The pathological diagnoses by age group are shown in **Table 3**. A total of 234 patients presented with constitutional symptoms; of these, 138 (59%) were diagnosed with cancer (Pearson Chi-Square value: 13.168, DF 1; P = 0.0000).

A total of 370 patients (77.9%) presented with generalized LAP (2 or more groups of Lymph nodes) and 102 patients (21.5%) presented with localized LAP; the extent of lymphadenopathy was unknown in 3 patients (0.6%). Patients with generalized LAP were more likely to have malignancy compared to those who presented with localized LAP (Pearson Chi-Square value: 67.201, DF 1; P = 0.0000). *The extent of lymphadenopathy was unknown in three cases. Please refer to **Table 4**.

Discussion

In a region with a high TB burden such as Saudi Arabia, it is very important to carry out appropriate evaluations when handling cases with LAP. In the eastern region of Saudi Arabia (Dammam and Alzahran), Al Tawfiq et al., reported TB lymphadenitis in cervical LAP is at 15.5%; however, this study was carried out in a high class patient population (Aramco employees and their dependents) [16]. In comparison, Al-Sohaibani et al. reported a rate of 28% in the same geographical region [17]. Another study found that although the rate of TB infection was reported to range from 14.2%-38% in the western region (Almadina, Jeddah and Makkah), an area with many expats and religious visitors [14, 15], the rate of TB lymphadenitis was only 14.2% [18].

The rate of TB infection was reported to be as high as 37.8% in the Central region (Riyadh) [19]. However, the rate of TB lymphadenitis in the present study was much lower at 8.8% compared to the rate of 37.9% reported by Abba et al. in the same region (central region, Riyadh) [19]. This cannot be explained solely by temporal aspects as the rate of TB infection is increasing generally across the Kingdom [12, 13]. However this difference may be partially explained by the fact that our cohort mostly consisted of Saudis who are known to have a lower incidence of TB compared to expats (non-Saudis) [12].

In a study reported from our institution by Memish et al., 80% of patients with TB lymphadenitis presented with cervical LAP; 36% had associated constitutional symptoms [20]. In the current study, only 20 patients (47.6 %) presented with cervical LAP and 17 (40.5%) presented with constitutional symptoms; there-

Table 3. Pathological diagnoses by age group

Diagnosis	Adults (N 377)	Pediatrics (N 98)
Reactive/non-specific lymphadenitis	96 (25.5)	41 (41.8)
Non-Hodgkin lymphoma	105 (27.9)	9 (9.2)
Hodgkin lymphoma	82 (21.8)	20 (20.4)
Tuberculosis lymphadenitis (non-necrotizing granulomatosis)	37 (9.8)	5 (5.1)
Solid tumors	17 (4.5)	Zero
Necrotizing granulomatosis	12 (3.2)	6 (6.1)
Other hematological malignancy	5 (1.3)	2 (2)
Kikuchi-Fujimoto disease	4 (1.1)	2 (2)
BCG lymphadenitis	Zero	6 (6.1)
Langerhans histocystosis	3 (0.8)	2 (2)
Sarcoidosis	3 (0.8)	1 (1)
Castleman disease	3 (0.8)	Zero
Brucellosis	3 (0.8)	Zero
Others	7 (1.9)	4 (4.1)

'Other hematological malignancy': Acute lymphoblastic leukemia, acute myeloid leukemia, multiple myeloma. 'Others': Dermatopathic lymphadenitis, neurofibroma, Kimura disease, cortical hyperplasia secondary to systemic lupus erythematosus (SLE) or rheumatoid arthritis, Human Immune deficiency virus (HIV) lymphadenitis.

Table 4. Extent of lymphadenopathy: cancer *vs.* non cancer

	No cancer N (%)	Cancer N (%)
Localized LAP (N = 102)	87 (85.3)	15 (14.7)
Generalized LAP (N = 370)	146 (39.5)	224 (60.5)

Pearson Chi-Square Value 67.201, DF 1, $P = 0.0000$. LAP: lymphadenopathy; Generalized LAP: two or more groups of lymph nodes.

fore, neither the non-cervical location of the LN, nor the absence of constitutional symptoms, excludes the possibility of TB lymphadenitis. Clinicians, as well as pathologists, should keep TB as a deferential option for all cases presenting with LAP, as the use of specific stains (such as the Ziehl-Neelson stain) is needed to confirm the diagnosis.

Variable rates of malignancy have been reported in the Saudi literature (28.8%-42%) among patients undergoing LN biopsies [16-19]. Hematological malignancies were reported to be more common than solid tumors in most of these previous studies, except for the study by Al-Tawfiq et al., which reported similar rates of hematological and solid malignancies [16]. In the current study, the overall rate of malignancy was 50.5%; this could be possibly explained by the fact that our cohort mostly consisted of adults. The clear predominance of hematological malignancies (92% of all malignant causes) is difficult to explain.

Generalized LAP can be secondary to self-limited viral illnesses such as infectious mononucleosis but usually indicates significant systemic disease such as serious viral infection, including acute HIV or connective tissue disorders. However, generalized LAP can also be associated with malignancy, including leukemias, lymphomas and advanced metastatic carcinomas [19, 21]. In the present study, patients presenting with generalized LAP were more likely to have cancer compared to those presenting with localized LAP. Those with associated constitutional symptoms, such as fever, nocturnal diaphoresis and weight loss, were also more likely to have cancer; among 234 patients presenting with constitutional symptoms, 138 (59%) were diagnosed with cancer.

Older age is known to be associated with a higher rate of malignancy in patients presenting with LAP [22, 23]. In the present study, malignant causes were more common in adults compared to pediatrics (209 (55.4%) *vs.* 31 (31.6%), respectively, $P = .0001$)). A clear understanding of patient demographics and exposure, associated systemic symptoms, abnormalities in laboratory data, along with lymph node location and description is vital in evaluating patients presenting with LAP.

Conclusions

TB lymphadenitis remains a significant medical problem in the central region of Saudi Arabia,

although this condition is less prevalent than before. Neither the non-cervical location of the LN, nor the absence of constitutional symptoms, exclude the possibility of TB lymphadenitis. Clinicians, as well as pathologists, should keep TB lymphadenitis as a deferential option for all cases presenting with LAP. Malignant conditions must be ruled out in patients presenting with LAP, especially in those who present with generalized LAP and those with associated systemic symptoms.

Disclosure of conflict of interest

None.

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