original research report

Epstein–Barr virus and Hodgkin lymphoma in Jordan

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BACKGROUND AND OBJECTIVES: This study aims to examine the possible association of Epstein–Barr virus (EBV) in Classical Hodgkin lymphoma (cHL) and to shed light on the epidemiology of Hodgkin lymphoma (HL) in Jordan.

PATIENTS AND METHODS: We examined 100 consecutive cases of HL for the presence of EBV in tumor cells by immunohistochemistry for latent membrane protein-1 (LMP-1). We collected patient data on age, sex and histologic subtype. We reviewed the pathological findings in each case and confirmed diagnosis.

RESULTS: Nodular lymphocyte predominant HL was diagnosed in 6% of the cases and these were negative for EBV LMP-1. Of the 94 cases of cHL, 65% were males, the most common subtype was nodular sclerosis (NS), representing 70% of the cases, and 45.7% of cHL (43% of all HL) cases were positive for EBV LMP-1. The positive cases were significantly related to age: ≤15 years and >51 years (p: 0.009 and 0.014 respectively), male gender (p: 0.03) and mixed cellularity (MC) subtype (p: <0.0001). In line with other developing countries, there also appears to be a trend towards a decreasing association of EBV with cHL and a subtype switch from MC to NS in Jordan.

CONCLUSION: The epidemiology of HL in Jordan and some developing countries is approaching that of developed countries.

Classical Hodgkin lymphoma (cHL) is known to be associated with Epstein–Barr virus (EBV) infection.[1–21] The frequency of this linkage varies both between countries as well as within the same country, and is presumed to be related to the socioeconomic status of the population. It also varies within each histologic subtype of cHL, gender and age at the time of diagnosis. The association between cHL and EBV is more likely to be found in developing countries than in more developed ones,[1,22] and is reported to decrease as the socioeconomic status of the population improves and approaches that of developed countries.[20–22]

Jordan is a developing country that is gradually adopting a western life style. This trend is reflected in general health issues, evident from the increasing prevalence of obesity, diabetes and colon cancer.[23] Previous studies from Jordan[24–26] and other Middle Eastern (ME) countries[12,13,16–18,28,29,30] have reported a varying range of EBV association with HL, ranging from 28% to 47% [24–26] in Jordan and up to 87% in other ME countries such as Iran.[26]

The aim of this study is to shed further light on the more recent epidemiology of Hodgkin's lymphoma and its association with EBV infection in Jordan.

MATERIALS AND METHODS

One hundred consecutive cases of HL diagnosed between 2006 and 2008, with available paraffin blocks were retrieved from the archives of the pathology department at King Hussein Cancer Center (KHCC). The original slides, inclusive of immunohistochemical studies, were independently reviewed by two senior pathologists to confirm diagnosis and histological subtype in each of the cases. Any discrepancy as to subtype was resolved by a consensus meeting.

Immunostaining for Epstein–Barr virus latent membrane protein-1 (LMP-1) (CS1-4, Cell Marque

Corp. Hot Springs, AR) was performed on all the cases using an automated platform (Ventana BenchMark, Ventana Medical Systems Inc., Tucson, AR), and employing standard protocols according to the manufacturer's recommendations. Immunostaining was considered positive if typical cytoplasmic and membranous staining was observed in Reed-Sternberg/Hodgkin cells regardless of the number of positively stained cells. Appropriate positive and negative controls were used for every case. The interpretation of immunostaining was conducted independently by two senior physicians. A consensus was reached on all cases.

Statistical analysis was performed using Chi square test or Fisher's exact test. A significance criterion of $p \leq 0.05$ was used in the analysis. All analysis was performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Classic Hodgkin lymphoma represented 94 (94%) of the 100 consecutive cases studied while 6 (6%) were diagnosed as nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). The age and sex of the patients stratified by the histological subtype are presented in Table 1.

There were 67 (67%) males and 33 (33%) females.

NLPHL

Of the 100 cases there were six cases of NLPHL (Table 1). All patients were males and their ages ranged from five to 42 years (median age, 24 years). All cases were negative for EBV LMP-1 immunostaining.

cHL

There were 94 patients with cHL out of the 100 HL cases studied. Of these, 63 (65%) were males and 33 (35%) were females (age range 3–73 years; median age, 24 years). The highest incidence was in the young adult group (16–50 years), constituting 66 (70%) of the 94 cases, followed by the 19 cases (20%) in the childhood group (≤15 years). 16 (84%) of these 19 children were boys.

Nodular sclerosis (NS) subtype was the most common subtype in all age groups ranging from 58% in the childhood group to 74% in the young adult group, and representing 70% of the entire group. Mixed cellularity (MC) was the second most common subtype and represented 28% of the entire group. In contrast to NS, MC was rarely encountered in females, with only 19% of the cases occurring in females compared to 42% of the cases in NS subtype. There were two patients with lymphocyte rich subtype and no cases of lymphocyte depletion HL.

Tumor cells were positive for LMP-1 in 43 cases (45.7%) of all cHL cases. The clinicopathologic features of the positive and negative cases are shown and compared in Table 2.

The EBV positive cases were more frequently encountered in the childhood (≤15 years) and elderly (>51 years) age groups, 68% and 78% positivity, respectively, in contrast to 35% in the young adult group (16–50 years); and this was statistically significant (Table 2). There were also more positive cases amongst males (54%) than females (30%), which was also statistically significant (p: 0.03). The histologic subtype was also a factor strongly linked to positivity, with 81% in MC vs. 30% in NS (p: <0.0001). Childhood cHL had 55% positivity in NS and 86% in MC.

All positive childhood cases were males except for a single case in a female.

DISCUSSION

This study shows that of all HL cases in Jordan the proportion of cHL is 94% and 6% in NLPHL. The latter is in agreement with the WHO Handbook[27] figure of 5%, and close to the same percentage as in the previous study from Jordan published in 2004 which showed a 3% rate,[24] and to the 6.7% recorded in a study from Kuwait[12] in 2003. This is, however, in sharp contrast to the 18% incidence data from Cairo, Egypt, published quite recently by Audouin et al.[22] and the 10% and 12% reported by Al-Salam from UAE[18] and Akhtar[30] from Saudi Arabia, respectively. The populations in Jordan, Egypt, UAE and Saudi Arabia are essentially the same, and the epidemiology of cHL is similar in those countries. There is no apparent reason for this discrepancy. However, the small sample size used in the studies could be a cause for speculation.

Three studies have examined the association of HL with EBV infection in Jordan.[24–26] In two of the studies, the number of patients was low, 16 and 28 respectively,[26,25] and there was a modest 64 patients in the third.[24] The proportion of EBV-associated cases was 28% in one study[25] but was 47% and 50% in the other two. The latter two values are similar to our findings (43%) for all HL patients. These figures appear to be more accurate than the 28% reported in 2004,[25] and are comparable to those of other ME countries, where the association ranges from 47% to 72%.[28] The discrepancy in the rate of association could be related to low numbers of patients and pediatric cases