Outcome of Patients With Positive Epstein-Barr Virus Serologic Status in the Absence of Nasopharyngeal Carcinoma in Hong Kong

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Objective: To evaluate the current clinical practice of follow-up and the outcomes of patients with raised Epstein-Barr virus (EBV) antibody levels but without pathological evidence of nasopharyngeal carcinoma (NPC) for a possible risk of developing NPC in the future.

Design: Retrospective review of prospectively collected database.

Setting: Tertiary referral otolaryngology center.

Patients: The study population comprised 66 patients (27 male and 39 female; median age, 43.5 [range, 9-78] years) who presented in 1997 with a positive EBV IgA viral capsid antigen titer but a negative nasopharyngeal biopsy result.

Main Outcome Measures: The detection of NPC and EBV seroconversion rate.

Results: Of the 66 patients studied, 14 had a positive family history of NPC. Fourteen patients (27%) were excluded because of loss of contact or refusal of follow-up. The median follow-up period of the remaining 52 patients was 54.5 months (range, 12-64 months). Of these 52 patients, 39 (75%) had initial nasendoscopic finding described as completely normal. During the follow-up period, NPC was diagnosed in 1 patient (2%) 18 months after first biopsy. The initial nasendoscopy and histological findings in this patient were normal despite the patient having a raised EBV IgA VCA titer of 1:640. Overall, the EBV serologic status of 36 patients (69%) reverted to normal within the studied period (median interval of 54.5 [range, 12-64] months).

Conclusions: In the median follow-up period of 54.5 months, only 1 patient (2%) developed NPC. A significant proportion of the patients seroconverted back to normal, none of whom developed NPC.

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THE INCIDENCE OF NASOPHARYNGEAL CARCINOMA (NPC) in Southeast Asia is notably higher compared with other parts of the world. In Hong Kong, NPC is the fourth most common cancer in men and the 10th most common in women and accounts for more than 5% of all cancer new cases. Patients with NPC regularly exhibit high levels of antibodies directed against EBV-specific antigens, in particular, IgA response to viral capsid antigen (VCA), compared with healthy populations. A positive serum IgA VCA titer indicates previous repeated infection by the virus or frequent reactivation of latent EBV in B cells. This has been used as a screening tool to identify subjects at high risk of NPC, as well as being a diagnostic criteria for undifferentiated NPC. In a serological mass survey in Wuzhou City, China, the incidence of NPC detection in patients with a positive EBV IgA VCA titer but an initial negative nasopharyngeal biopsy result during their 4-year follow-up was 1.5%. In the Taiwanese population, an increase in the difference of the cumulative incidence of NPC between seropositive and seronegative subjects was associated with the duration of follow-up. It was suggested that the increase in the cumulative incidence among seronegative subjects 9 years after enrollment may be explained by subsequent seroconversion during the follow-up period.

Although Hong Kong is geographically part of the Guangdong province in southeast China, with 90% of the population Cantonese in origin, the risk of Hong Kong patients with raised EBV antibodies but without pathological evidence of NPC later developing NPC remained unclear. The aim of this study was to evaluate the current clinical practice of fol-
low-up and the outcome of this group of patients in Hong Kong.

### METHODS

A retrospective study was conducted on patients who presented to the University of Hong Kong Medical Centre with positive EBV IgA VCA serologic status, whose initial nasopharyngeal biopsy results were negative. Patients were identified from the hospital patient database during the year of 1997. Patients were followed up at 6- to 12-month intervals. During each visit, the patients underwent endoscopic examination of the nasopharynx under local anesthesia, with a biopsy specimen taken when NPC is suspected. Blood samples were routinely examined for IgA antibodies against EBV viral capsid antigen. Data were retrieved from computer records and case notes review. Patients with follow-up information of less than 4 years were recalled for clinical assessment.

### RESULTS

A total of 66 patients in 1997 with a positive EBV IgA VCA titer but negative nasopharyngeal biopsy result were identified. Fourteen patients were excluded owing to loss of contact or refusal to follow-up. The remaining 52 patients (21 male and 31 female) had a median age of 43.5 (range, 9-78) years. Fourteen patients had a positive family history of NPC. The initial average EBV IgA VCA titer was 1:106.1 (median, 1:40 [range, 1:10-1:640]). Initial nasendoscopic examination was described as normal in 39 patients (75%), with nasopharyngeal swelling in 7 patients (14%), irregular surface in 3 patients (6%), adenoids in 2 patients (4%), and nasal polyp in 1 patient (2%). Normal histologic status was identified in 38 patients (73%), lymphoid tissue in 13 patients (25%), and focal squamous metaplasia in 1 patient (2%). The median duration of follow-up was 54.5 (range, 12-64) months.

During this period, 1 patient died of other medical reasons 12 months after his first nasopharyngeal biopsy. At 18 months after first biopsy, 1 case (2%) of NPC was diagnosed. This involved a 72-year-old man with no family history of NPC, who presented with persistent right-sided otitis media and an EBV IgA VCA titer of 1:640. Despite the persistence of his symptoms and significantly raised level of antibodies, findings from his nasopharyngeal examination remained normal even at the time of histological diagnosis. His subsequent computed tomographic findings were consistent with T1 N0. Four other patients also had a high titer (1:640). They presented initially with otitis media, neck node, meningitis, and mononeuritis. None of these 4 patients developed NPC during follow-up.

Overall, EBV IgA VCA titers of 36 patients (69%) reverted to normal during the study period (median revision interval, 53.5 [range, 6-64] months). The Table gives the distribution of EBV IgA VCA titers at the time of screening and the proportion that reverted to normal. Statistical analysis showed no association between initial titer and the chance of reverting to normal (χ² test for trend, P = .71; Fisher exact test, P = .94).

### COMMENT

In the present study, 2% of the patients with a positive EBV IgA VCA titer subsequently developed NPC. This figure is similar to the 1.5% reported in the study by Zeng et al. Hence, it was believed that despite the smaller number of patients in our series, the studied population is representative. Although the mean EBV IgA VCA titer of 106.1 within our group of patients screened for NPC was lower than the mean titer of 132.9 in another group of patients with NPC in Hong Kong, it is much higher than the mean titer of 8.4 in a randomly selected group of patients without NPC, suggesting that our subgroup of patients may bear a higher risk of developing NPC compared with the population with a normal EBV IgA VCA titer.

The overall incidence of seronegative patients subsequently developing NPC was previously reported to be 0.15%, and they were 22 times less likely to develop NPC compared with patients with a positive EBV IgA VCA titer. However, it was not clear whether any of these seronegative patients became seropositive at a later date and whether they subsequently developed NPC as a result of delayed undetected seroconversion. The EBV IgA VCA antibody status of over two thirds of our patients reverted to normal during the study period; however, this was found not to be related to initial EBV titer. Although none of these patients developed NPC within the study period of up to 5 years after the first biopsy, the EBV serologic status of a proportion of these patients reverted to normal at a much later part of the follow-up period. Therefore, they have not been followed up long enough after reversion to determine their risk to subsequently developing NPC.

### CONCLUSIONS

The risk of Hong Kong patients with positive EBV IgA VCA titer of developing NPC after an initial normal biopsy result was 2%. Although there was a significant proportion of patients with a positive EBV IgA VCA titer that reverted to normal, it remains unclear of the subsequent risk of this subgroup of patients later developing NPC. Given the small number of patients studied with a positive EBV IgA VCA titer but initial negative nasopharyngeal biopsy results, further studies are warranted to determine the risk of subsequent NPC.
ryngeal biopsy result, a larger prospective patient group will be required to further evaluate these findings.

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REFERENCES


