Role and Impact of Human Papillomavirus in Cervical Metastasis From Unknown Primary

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ABSTRACT

Introduction: The role of Human Papillomavirus (HPV) as a causative factor in cervical metastasis from an unknown primary (CMUP) and the impact of the virus on survival is unclear. The goal of this study was to compare outcomes of patients with HPV-associated CMUP to those of patients without evidence of HPV.

Study Design: Retrospective cohort.

Methods: Patients diagnosed with metastatic squamous cell carcinoma (SCC) with unknown primary after a thorough workup during the last 15 years were studied. Demographic, histological, and survival data were compared on p16 status.

Results: Nineteen patients met inclusion criteria and had specimens suitable for p16 testing. Of these, 14 were positive for p16 (74%) and 5 were negative (26%). There were no differences between patients with respect to age or race. Patients with HPV-induced head and neck cancers had improved survival compared to those whose cancer is not caused by HPV, and HPV-induced head and neck cancers are thought to be more radiosensitive than those related to traditional risk factors.

Conclusions: The incidence of p16 positivity in CMUP is similar to that reported for oropharyngeal SCC. Our data suggest that HPV is a common etiologic agent in CMUP and, similar to other anatomic subsites within the head and neck, p16 positivity appears to confer a better prognosis.

INTRODUCTION

Human papillomavirus (HPV) is causally associated with cancers of the uterine cervix, anogenital tract, and head and neck. For head and neck cancers, it is estimated that HPV infection plays an etiologic role in up to 80% of cases of oropharyngeal squamous cell carcinoma (SCC), primarily in patients without traditional risk factors including tobacco and alcohol. Patients with HPV-induced head and neck cancer generally have improved survival compared to those whose cancer is not caused by HPV, and HPV-induced head and neck cancers are thought to be more radiosensitive than those related to traditional risk factors.

Cervical lymph node metastasis with unknown primary (CMUP) is a relatively uncommon subset of head and neck malignancy in which no primary site can be identified even after a thorough workup.1 Histologically, SCC represents 75–90% of these cases.1 The relationship between HPV infection and CMUP has not been studied. The purpose of this study is twofold: (1) To determine the prevalence of HPV-induced malignancy among patients with CMUP, and (2) to compare the survival of patients with HPV-induced malignancy to that of patients whose cancer is not caused by HPV.

PATIENTS & METHODS

Patients with SCC CMUP presenting between 1994 and 2010 were included. Exclusion criteria included a history of cutaneous SCC of the head and neck, metastasis to intraparotid lymph nodes, and histopathology other than SCC.

Patient Characteristics

A total of 35 patients (31 men, 4 women) were diagnosed with CMUP during the study period. Of these, 19 patients (54%) had archived specimens suitable for p16 immunohistochemical analysis available. Demographic data is displayed in Table 1.

Diagnosis workup

All patients underwent a thorough history and physical examination, fine needle or excisional lymph node biopsy, anatomic imaging, and panendoscopy (direct laryngoscopy, bronchoscopy, and esophagoscopy).

Immunohistochemistry

All available pathology specimens were tested by immunohistochemical methods for increased expression of p16, an endogenous cell cycle protein that is overexpressed in cells transformed by HPV infection.

Endpoints and statistics

Endpoints were disease-free survival and overall survival (death from any cause). Baseline characteristics of the p16-positive and p16-negative groups were compared using Chi-squared tests for nominal variables and unpaired t-tests for continuous variables. Actuarial tumor response and survival data were analyzed using Kaplan-Meier product limit estimates. A significance level of p = 0.05 was used.