COX-2 Overexpression in Sinonasal Inverted Papilloma

Jeffrey D. Suh MD1; Fernando Palma-Diaz MD2; Sunita Bhuta MD2; Marilene B. Wang, MD1

1Department of Head and Neck Surgery, UCLA School of Medicine
2UCLA Department of Pathology and Laboratory Medicine

ABSTRACT

Background/Aims:
Inverted papilloma (IP) is a benign, but locally aggressive neoplasm of the nasal cavity and paranasal sinuses. The mainstay of treatment of IP is surgical resection, but high rates of tumor recurrence have been reported. Cyclo-oxygenase-2 (COX-2) has been found to be overexpressed in many tumors and has been used successfully as a therapeutic target. The goal of this study is to highlight COX-2 expression in sinonasal inverted papilloma.

Methods:
Immunohistochemistry for COX-2 was performed on consecutive IP samples obtained during definitive resection. The intensity of staining was evaluated by pathologists blinded to the clinical features and outcomes. A positive stain was defined as having 10% or more of tumor cells exhibiting immunoreactivity.

Results:
There were 6 tumor samples from 4 females and 2 males. Mean age was 42 years (range 18-73). Tumor locations included: Sphenoid(1), ethmoid(2), nasal septum (1) and maxillary(2) sinuses. 5/6 (83%) of the tumors stained positive for COX-2.

Conclusion:
COX-2 overexpression was identified in 83% of cases of IP in this study. Larger studies are necessary to identify the true incidence of COX-2 expression for this tumor. Pharmaceuticals targeting COX-2 may eventually provide an additional therapeutic option for select cases of recurrent or unresectable IP.

INTRODUCTION

Cyclo-oxygenase (COX) is the rate-limiting enzyme in prostaglandin synthesis. The enzyme catalyzes the conversion of arachidonic acid to prostaglandin endoperoxide (prostaglandin H2). There are two isoforms of cyclo-oxygenase, COX-1 and COX-2. COX-1 is typically a constitutive enzyme expressed in most tissues, which is responsible for the production of prostaglandins that mediate normal physiological functions such as the maintenance of the integrity of gastric mucosa and the regulation of renal blood flow.1

In contrast, COX-2 is undetectable under normal conditions in most cells, but elevated levels are found during inflammation and in many cancers.2-4 It has been implicated in tumorigenesis in a number of cancers, including colon, lung, esophageal, breast, and head and neck cancers.2-5 To date, at least five mechanisms by which COX-2 contributes to malignancy have been identified including: (1) inhibition of apoptosis; (2) increased angiogenesis; (3) increased invasiveness; (4) modulation of inflammation/immuno-suppression; (5) conversion of procarcinogens to carcinogens.1,4 Recent evidence suggests that COX-2 may play a role in the development and progression of recurrent respiratory papillomatosis (RRP).5,6 COX-2 inhibitors have shown promise as a novel, well tolerated, adjunctive treatment modality for select malignancies, and more recently, for RRP.1,2

Sinonasal inverted papilloma (IP), like RRP, is a benign but locally aggressive tumor that can have a high rate of recurrence, especially when the tumor involves the orbit or intracranial space. In some cases, achieving negative surgical margins is difficult without significant morbidity. These patients are usually subjected to frequent surgeries to debulk the tumor when they become symptomatic. However, this approach is less than ideal due to the risk of IP undergoing transformation to carcinoma.6,8 Radiation therapy for inverted papilloma has been described for aggressive or recurrent tumors, but the data supporting its use for a majority of IP is limited.

METHODS AND MATERIALS

Tumor samples were obtained from patients with inverted papilloma undergoing surgery at the University of California, Los Angeles (UCLA) Medical Center from January 2012 to October 2012 by a single surgeon (JDS). Use and collection of these tissues was approved by the UCLA Institutional Review Board. Hematoxylin and eosin stains confirmed the diagnosis of IP. Samples reserved for immunohistochemistry were fixed in 10% buffered formalin, paraffin-embedded and processed by conventional methods. Six consecutive patients with IP underwent tumor resection.

Immunohistochemistry:
For immunostaining, standardized and controlled protocols were followed using commercially available antibodies. The slides were incubated with the COX29 monoclonal anti-COX-2 antibody from Zymed (Grand Island, New York, USA) at a 1:400 dilution for 30 minutes following heat induced epitope retrieval in citrate buffer. Visualization was achieved with Vision Biosystem PowerVision plus Poly-HPR detection system. The slides were then counterstained with Dako hematoxylin for 1 minute. A negative control from a patient with CRS without inverted papilloma was also performed. Slides were reviewed by two pathologists (FPD and SB) blinded to the clinical features and outcomes. The intensity of staining was then evaluated as 1+ (weak), and 2+ (strong). A positive stain was defined as having 10% or more of tumor cells exhibiting immunoreactivity.

RESULTS

There were 6 tumor samples evaluated during the study period for the case series. There were 4 females and 2 male. Mean age was 42 years (range 18-73). See Table 1 for Patient Demographic Information and Tumor location. Two patients had prior recurrences of IP prior to presentation (Patients 2,6). Other cases presented after biopsy.

The 6 patients underwent endoscopic or endoscopically-assisted resections with negative margins. Average follow up time for patients in this study was 101 days (range 29 -157 days). There were no recurrences in this short follow up time period. No cases demonstrated malignancy or dysplasia on final pathology. 5/6 (83%) of the IP samples stained positive for COX-2. (Figure 2) Of these, 3 stained strongly for COX-2, and 2 were weakly positive. (Table 1)

CONCLUSIONS

This report documents COX-2 overexpression in cases of sinonasal inverted papilloma without dysplasia or malignancy. These preliminary results prompt a reconsideration of COX-2 inhibitors as a potential therapeutic target for unresectable or recalcitrant tumors.

REFERENCES