Conjunctival papilloma caused by human papillomavirus type 11 treated with systemic interferon in a five-year-old boy

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Conjunctival papilloma is a benign tumor of the conjunctival mucosa. In childhood, papilloma represents 7-10% of conjunctival tumors. Human papillomavirus (HPV)-6 and HPV-11 are the major HPV types responsible for conjunctival lesions.

A five-year-old boy with a two-year history of conjunctival papilloma caused by HPV type 11 treated with systemic interferon alpha is reported and the literature is reviewed.

Key words: conjunctival papilloma, human papilloma virus type 11, human papillomavirus type 27, systemic interferon, topical interferon.

Infectious agents contribute to around 18% of human cancers worldwide. The role of infectious agents in ocular adnexal neoplasms is most likely as a cofactor to genetic and environmental risk factors. Several microorganisms have a pathogenic role in different ocular adnexal malignancies including human immunodeficiency virus in conjunctival squamous carcinoma; human herpes simplex virus-8 in conjunctival Kaposi sarcoma; Helicobacter pylori, chlamydia and hepatitis C virus in ocular adnexal mucosa-associated lymphoid tissue lymphomas; and human papillomavirus (HPV) in conjunctival papilloma. Conjunctival papilloma is a benign tumor of the conjunctival mucosa. In childhood, papilloma represents 7-10% of conjunctival tumors. There is a possible role for HPV in this tumor. HPV-6 and HPV-11 are the major HPV types responsible for the benign conjunctival lesions. The tumor can be treated either by surgical excision or cryotherapy, but the recurrence rate is unfortunately high.

A five-year-old boy with a two-year history of conjunctival papilloma caused by HPV type 11 treated successfully with systemic interferon alpha is reported and the literature is reviewed.

Case Report

A five-year-old boy was referred by an ophthalmologist for evaluation of a lesion on his lower eyelid. The biopsy of the lesion revealed benign conjunctival papilloma with hyperplasia without signs of dysplasia (Fig. 1). HPV type 11 was detected by polymerase chain reaction (PCR) and DNA sequencing method. The ophthalmologist had treated him with a combination of surgical excision and cryosurgery. Despite several repeated procedures [local excision (x2) and cryosurgery (x3)], the patient experienced recurrences. Due to local treatment failure, the patient was then referred to pediatric oncology for a medical therapy. Examination revealed a soft, nodular, pedunculated mass with an irregular surface on the lower eyelid and conjunctiva (Fig. 2). Physical examination was otherwise normal. No history of cutaneous wart at extraocular sites was reported. His family history was
negative. Routine complete blood cell count, blood biochemical tests and urine analysis were found to be normal. The patient was treated with interferon alpha $3 \times 10^6$ U/m², subcutaneously, three times per week for six months. During the therapy, the patient experienced no side effects. Liver enzymes and complete blood count tests were checked periodically. The patient was followed every two weeks initially and then every four weeks. A complete response was achieved following a six-month interferon treatment and at the end of the treatment, the papilloma disappeared. A cutaneous wart appeared six months later on the forearm. Histopathologic analysis confirmed the diagnosis (Fig. 3). HPV genotyping showed positivity for HPV type 27. It was treated successfully with cryosurgery. No papilloma recurrence was encountered during the two-year follow-up period.

Discussion

Human papillomavirus is a DNA virus from the Papovavirus class and has at least 85 well-documented genotypes. Although the skin is the most common extragenital HPV infection site, lesions can occur within the mouth, esophagus, larynx, trachea and conjunctiva. Sjö et al. investigated normal conjunctival tissue for the presence of HPV and found all normal conjunctival biopsy specimens to be...
HPV-negative. A number of HPV types are classified as low-risk type because they rarely progress to invasive cancer. Although HPV types 6 and 11 are identified as low-risk types, Köning et al. detected HPV-6 and HPV-11 in 10 out of 60 head and neck carcinomas. They reported that HPV presence was correlated with p16 immunoreactivity. Low-risk HPV types 6 and 11 and high-risk HPV types 16 and 33 have been identified in conjunctival papilloma (Table I). Transmission to the conjunctiva may occur at birth via an infected birth canal or via ocular contact with contaminated hands. In our patient, HPV type 11 was found in conjunctival papilloma. There were no genital warts or mucocutaneous papillomatous lesions. Low-risk HPV types 6 and 11 cause most of the benign warts of the female genital tract. HPV has been found in normal smears with a prevalence of up to 25%. It might be possible that the patient was infected with HPV-11 from his mother’s genital tract at birth, though she had a normal gynecologic exam. HPV type 27 is a low-risk type and is generally associated with benign warts. It is common in childhood, most often found at non-genital sites, and frequent skin-to-skin contact increases the likelihood of transmission.

Polymerase chain reaction (PCR) and DNA sequencing technique are reliable for the detection of HPV in conjunctival papilloma. By genotyping, the conjunctival mucosa was infected with HPV-11, while HPV-27 was determined on the forearm.

The classic approach to the treatment of conjunctival papilloma includes surgical resection and cryosurgery. If the margins are not free after resection, the recurrence rate is high. Papilloma may resolve without treatment. The rate of spontaneous remission is influenced by viral types, host immune status, and extent and duration of warts. Interferon therapy is an adjunct therapy to surgical excision of recurrent or multiple lesions. The use of interferon in HPV infections and malignancies has been reported to show considerable benefit. Conjunctival papilloma can be treated with both systemic and topical interferon. Lass et al. treated five papilloma patients with recurrent, multiple lesions with systemic interferon. Treatment was started after surgical excision and two patients did not show recurrences. They concluded that systemic interferon was not curative. Systemic interferon has many side effects. In pediatric patients, the most frequent adverse events related to interferon treatment include flu-like symptoms, gastrointestinal system disorders, nausea, and vomiting. Neutropenia and thrombocytopenia have also been reported. The patients should be monitored closely with periodic clinical and laboratory evaluations. Since the history of frequent surgical excision and cryosurgery negatively affected compliance of the current patient’s parents, we preferred systemic interferon alpha therapy in our patient. There were no side effects during the six-month follow-up and we obtained good results at the end of the therapy. Unfortunately, a new HPV infection appeared on the forearm six months later. Interferon therapy did not prevent the occurrence of a new HPV infection in our patient. Some HPV genotypes have a greater replicative capacity than others. High levels of replication might contribute to resistance to interferon treatment.

Small-to-medium sized conjunctival papillomas can be treated with topical interferon. Side effects of topical interferon are mild conjunctival hyperemia and follicular conjunctivitis. Schechter et al. treated two conjunctival papilloma patients with topical interferon alpha. The patients used topical interferon until clinical resolution was achieved. No recurrence was observed during the follow-up period. de Keizer et al. treated two papilloma patients with topical interferon. In one of the patients, topical interferon was started and followed by systemic interferon alpha. They concluded that topical interferon can be used as adjuvant therapy in recurrent lesions.

Human papillomavirus vaccine is now available for prevention of HPV-associated dysplasias and neoplasias, including cervical cancer, genital warts and precancerous genital lesions. Vaccination is approved for females aged 11 to 12 years. Except in a few countries, it is generally not recommended for boys or men. Quadrivalent HPV vaccine will be more helpful for ocular disease. Due to the possible role of HPV in conjunctival squamous carcinoma, the vaccination program may have an effect on the occurrence of ocular cancers. HPV vaccine may provide a potentially promising
TABLE I. Review of Published HPV DNA Type Studies in Conjunctival Papilloma

<table>
<thead>
<tr>
<th>References</th>
<th>Technique</th>
<th>HPV types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saegusa et al.</td>
<td>ISH, PCR</td>
<td>HPV-16</td>
</tr>
<tr>
<td>Nakamura et al.</td>
<td>ISH, PCR</td>
<td>HPV-6</td>
</tr>
<tr>
<td>Palazzi et al.</td>
<td>ISH, PCR</td>
<td>HPV-11</td>
</tr>
<tr>
<td>Sjö et al.</td>
<td>PCR</td>
<td>HPV-6/11</td>
</tr>
<tr>
<td>Gallagher et al.</td>
<td>PCR</td>
<td>HPV-6/11/16</td>
</tr>
<tr>
<td>Eng et al.</td>
<td>PCR</td>
<td>HPV-6/11</td>
</tr>
<tr>
<td>Minchiotti et al.</td>
<td>PCR</td>
<td>HPV-11</td>
</tr>
<tr>
<td>Sjö et al.</td>
<td>PCR</td>
<td>HPV-6/11/45</td>
</tr>
<tr>
<td>Buggage et al.</td>
<td>PCR</td>
<td>HPV-33</td>
</tr>
<tr>
<td>Mäntyjärvi et al.</td>
<td>ISH</td>
<td>HPV-11</td>
</tr>
<tr>
<td>Our case</td>
<td>PCR</td>
<td>HPV-11</td>
</tr>
</tbody>
</table>

ISH: In situ hybridization. 
PCR: Polymerase chain reaction. HPV: Human papillomavirus.

approach for the control of other lethal HPV-associated malignancies in addition to genital cancers12.

In conclusion, systemic interferon therapy did not prevent the occurrence of a new HPV infection in our patient. Due to its high cost and considerable side effects, systemic interferon is not the first treatment option. Topical interferon might be a better treatment option for small-sized papilloma lesions.

REFERENCES


