Recurrent laryngeal papillomatosis: successful treatment with human papillomavirus vaccination

Peter Mudry,[1] Martin Vavrina,[1] Pavel Mazanek,[1] Michaela Machalova,[2] Jiri Litzman,[3] Jaroslav Sterba[1,4]

[1]Department of Paediatric Oncology, University Children's Hospital Brno, Brno, Czech Republic
[2]ENT Department, University Children's Hospital Brno, Brno, Czech Republic
[3]Department of Clinical Immunology and Allergology, St. Anne's University Hospital, Brno, Czech Republic
[4]Masaryk University School of Medicine, Brno, Czech Republic

Correspondence to
Peter Mudry, Department of Paediatric Oncology, University Children's Hospital Brno, Cernopolni 9, 662 63 Brno, Czech Republic; pmudry@seznam.cz

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ABSTRACT

The authors describe the case of a 5-year-old girl with recurrent laryngeal papillomatosis (RLP) due to human papillomavirus (HPV) type 11, who required frequent surgical treatment. Complete recovery occurred after HPV vaccination (Gardasil). Confirmed remission of RLP has continued during the 17 months of follow-up since vaccination. The authors conclude that HPV vaccination may represent a new therapeutic option in this situation.

CASE REPORT

The index case was born at term following an uncomplicated labour. Her mother had no clinical signs of human papillomavirus (HPV) infection. Psychomotor development was normal and the child had occasional mild upper respiratory tract infections. At the age of 2 years she gradually developed a hoarse voice and was referred to the local hospital. After ear-nose-throat (ENT) clinical examination and direct optical laryngoscopy, the patient was diagnosed with laryngeal papillomatosis and surgical laser ablation of papillomas was performed. Subsequent histological examination of tissue showed papillary structures covered by acanthotic squamous epithelium with mixed inflammatory cells in stroma. Final pathological diagnosis was squamous papilloma with mild dysplasia.

The patient was frequently seen by an ENT specialist during follow-up. Within 2 years of diagnosis there were six relapses with development of papillomas necessitating surgical treatment. These interventions were performed using laser ablation. Intervals between treatments shortened so that the shortest disease-free period was only 3 weeks. The last surgical excision was performed using surgical pliers under microscope control.

DNA from a biopsied specimen was isolated by means of a QIAamp DNA Mini Kit (tissue protocol) according to the manufacturer's handbook (QIAGEN, Hilden, Germany). Extracted DNA was amplified in a PTC 200 PCR thermocycler (MJ Research, Waltham, Massachusetts, USA). As an internal control, a 110 bp long fragment of the human β-globin gene was amplified using PC03/PC04 primers. Positive β-globin amplification showed that the sample contained enough DNA and that no PCR inhibitors were present. HPV DNA was detected by PCR using GP5+/GP6+ primers specific for the L1 region. Genotyping was performed by reverse line blot hybridisation (RLB), which permits the detection of 37 HPV types in a single assay.[1] Genotyping in our case showed HPV type 11.

Immunological tests found no defects in humoral or cellular immunity. ELISA was used to test for anti-HPV antibodies using virus-like particles composed of capsid antigen L1 produced in a baculovirus expressing system in insect cells. No antibodies were found against HPV types 6, 11, 16, 18, 31 or 33. All HPV diagnostic procedures were undertaken in the National Reference Laboratory for Human Papillomavirus in The Institute of Hematology and Blood Transfusion, Prague.

The progressive course of the patient's disease led us to consider stimulating an immune response to HPV-11 as this might have a better chance of achieving long term remission compared to standard adjuvant treatments (such as cidofovir). We chose vaccination using a commercially approved vaccine with anti HPV-11 activity (GARDASIL, Merck, New Jersey, USA; regional brand name SILGARD in the Czech Republic). We used a three-dose schedule of vaccination (at 0, 2 and 6 months), with the first dose given 1 month after the last surgical excision.

The overall clinical picture and the course of disease changed markedly after vaccination. Since administration of the first vaccine dose, the patient has not experienced any episodes of voice hoarsening and repeated laryngoscopic examinations have found no recurrent papillomas. Two months after the third (and last) vaccination we checked anti-HPV antibodies and detected anti HPV-6 and anti HPV-11 antibodies in plasma.

Subsequent immune status study showed increased levels of IgM antibodies (1.88 g/l; reference range 0.4–1.6 g/l) and normal absolute CD3+ (3.04×10^9/l; range 0.7–4.2), CD4+ (1.9×10^9/l; range 0.3–2.0) and CD8+ (0.93×10^9/l; range 0.3–1.8) T cell counts. At the time of writing, our patient has had no evidence of papillomatosis for 17 months. This is her longest disease-free period and her voice has regained normal physiological tone.

DISCUSSION

Recurrent laryngeal papillomatosis (RLP) in children is a rare, chronic and potentially devastating disease significantly affecting quality of life. Disappointing treatment results with laser surgery are not uncommon and encourage exploration of new therapeutic options. For decades non-specific immunotherapy with interferon α has been one of the few options. However, treatment with interferon α has a risk of lesion relapse after discontinuation of treatment. Furthermore, interferon treatment also has significant systemic toxicities.[2] Some evidence of the efficacy of antiviral agents as adjuvant agents in the management of RLP in

children and/or adults has been also published.[3 4] Adjuvant intralesional treatment with bevacizumab showed some efficacy in prolonging the time between treatments and therefore reducing the number of treatments per year in children with severe RLP.[5] All described options have limited efficacy or significant toxicities and/or need surgical intervention.

Recent research has described the central importance of the CD4 T cell population in the control of HPV infection.[6] We were aware that treatment with HPV vaccine may not lead to a cellular immune response as most reports describe the vaccine as producing serum neutralising antibody to HPV major capside protein L1. Given the absence of anti HPV-11 antibodies in our patient, we decided to try to improve her HPV-11 antibody production and also to stimulate T cell-dependent specific anti-HPV immunity. Our evaluation of immune response after vaccination was limited to only general humoral and cell immunity together with evaluation of specific anti-HPV antibodies. Of course, this does not provide any proof of anti-HPV T cell activity. Moreover, a different surgical technique was used during the last intervention, so we do not know for definite which action was curative for this child.

Previously published case reports described stabilisation of RLP with small residual papilloma after HPV vaccination in a 2-year-old boy and in an adult.[7 8] As in these published cases, we also observed a fundamental change in disease course after vaccination with HPV vaccine, but in contrast to them, our patient was in RLP remission after the last surgical excision. To our knowledge, this disease remission lasting 17 months after HPV vaccination is the longest reported in the literature to date.

We demonstrated that vaccination using an off-label indication for an already approved drug can induce prolonged clinical remission of this otherwise devastating condition. Obviously, more extensive multicentre studies are needed to fully assess the potential benefit of this therapeutic approach.[7 9] While we await these studies, a centralised international database of similar cases would be a good first step towards understanding and monitoring this condition.

Competing interests None.

Patient consent Obtained.

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