

CASE REPORT

UNCONTROLLED HUMAN PAPILLOMA VIRUS INFECTION IN A 28-YEAR-OLD MAN LEADING TO DEATH – CASE REPORT AND REVIEW OF LITERATURE

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Recurrent respiratory papillomatosis is an increasingly common disease which leads to organic and functional limitations. Clinical symptoms depend on the location and extent of the papillomatosis. They include hoarseness, cough, and, in some cases, significant narrowing of the respiratory and digestive tracts.

The present report describes a fatal case of a young man (28 years old) who developed a very dynamic papilloma infection of the larynx, which spread to the trachea, the oesophagus, the soft tissues of the neck, and the mediastinum. Multimodal treatment did not stop the progression of the disease.

The papillomatous lesion was removed with a CO₂ laser used in a Kleinsasser microlaryngoscopy and under a microscope using an electrocoagulation loop with argon plasma during the gastroscopy. Antiviral treatment with cidofovir was introduced, as well as in further follow-up radiotherapy. Congenital or acquired immunodeficiency was also excluded.

Despite multimodal treatment, successful eradication of the infection was not possible. In our case, aggressive progression of the disease was observed. We were unable to confirm malignant transformation. Papillomatosis was the only disease, and its aggressive development led to the patient's death. In the case of aggressive, uncontrolled progression – when the infiltration spreads beyond the larynx and the hypopharynx – there are no alternative treatment methods that would lead to an effective cure.

Key words: recurrent papillomatosis, CO₂ laser, laryngeal cancer, interdisciplinary treatment.

Introduction

Recurrent respiratory papillomatosis is an increasingly common disease which leads to organic and functional limitations. The disease is caused by the human papilloma virus (HPV). Most patients (90%) with respiratory papillomatosis are infected with HPV type 6 and 11 [1, 2], which are the same types of HPV associated with the development of

genital warts. HPV types 16, 18, 31, 33 are much rarer in the respiratory tract [3, 4]. The development of papillomatosis in adults is caused by the reactivation of slowly progressing latent HPV or by infection during oral-genital sexual contact. Papillomatosis can be divided into juvenile-onset and adult-onset. In some adult-onset cases, the disease can lead to the development of cancer (*Carcinoma planoepitheliale verrucosum*).

Clinical symptoms depend on the location and extent of the papillomatosis, and include increasing hoarseness, coughing, and, in some cases, significant narrowing of the respiratory and digestive tracts. As a result of infection development, the patient has difficulty in breathing and swallowing. The average time between the first appearance of symptoms and diagnosis usually ranges from 1 to 8 years [1]. In most cases, the disease affects the larynx. But it can also spread beyond that organ in some patients (6-17% of cases) [1]. Apart from the larynx, other commonly affected organs include the oral cavity, the trachea, and the bronchi. Less commonly, the disease can involve the lungs or the oesophagus.

The present report describes the case of a young man who developed a very dynamic papilloma infection of the larynx, which spread to the trachea, the oesophagus, the soft tissues of the neck, and the mediastinum. Multimodal treatment did not stop the progression of the disease. Despite interdisciplinary treatment, successful treatment of the infection and its consequences was not possible due to the aggressive progression of the disease.

Case description

A 28-year-old man complaining of hoarseness and discomfort on swallowing was admitted to the Department of Head and Neck Surgery and Oncological Laryngology at our institution. Clinical tests revealed a papillomatous tumour in the interarytenoid area, partially covering the back sections of both vocal folds. The ENT examination did not reveal any additional abnormalities. The oral, oropharyngeal, epipharyngeal and hypopharyngeal mucous membranes were clear.

Diagnostics

The imaging protocols (CT scan with contrast) did not reveal any lesions in the larynx or hypopharynx. Vocal folds were symmetrical, with no pathological contrast enhancement, and slightly increased sclerosis of the arytenoids (arytenoid cartilages). We also observed mildly increased enhancement in the mucous membrane around the posterior commissure (Figs. 1, 2).

The ultrasound examination revealed single (sonographically) reactive lymph nodes in the fat tissue, measuring up to 12 mm, located bilaterally along the vessels and under the sternocleidomastoid muscle.

Microlaryngoscopy (Kastenbauer method) was conducted to assess the extent of the changes and to collect samples for histopathology. The examination showed a mulberry growth in the interarytenoid area, a normal epiglottis, symmetrical, smooth vocal folds, and clear pyriform sinuses. The postcricoid area and

oesophagus mouth were free of pathological lesions. Histopathology confirmed the diagnosis of planoepithelial papilloma, a lesion of viral aetiology. Immunohistochemical studies confirmed the presence of HPV. The antibody clone used for detection was against HPV 6, 11, 16, 18. Further molecular studies did not reveal any malignant subtype (Figs. 3, 4).

Treatment

The entire macroscopically visible papillomatous lesion was removed from macroscopically healthy tissues in the interarytenoid area and oesophageal entrance. A CO₂ laser was used in a Kleinsasser mi-

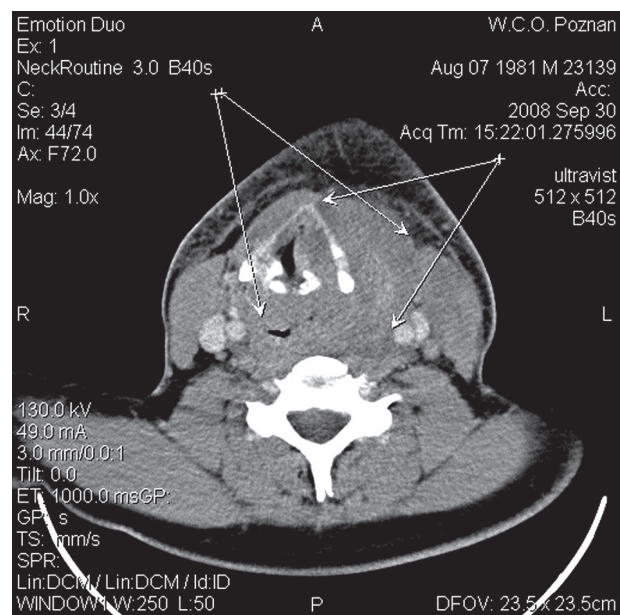


Fig. 1. CT horizontal scan of the papillomatous lesion in the neck

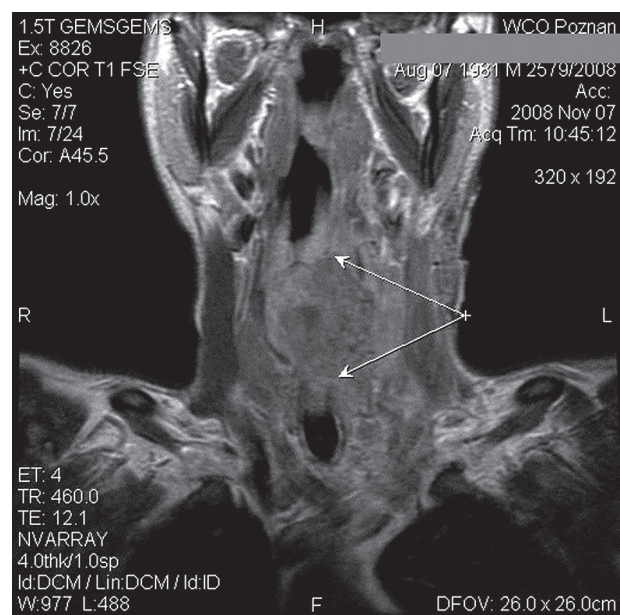


Fig. 2. CT frontal scan of the papillomatous lesion

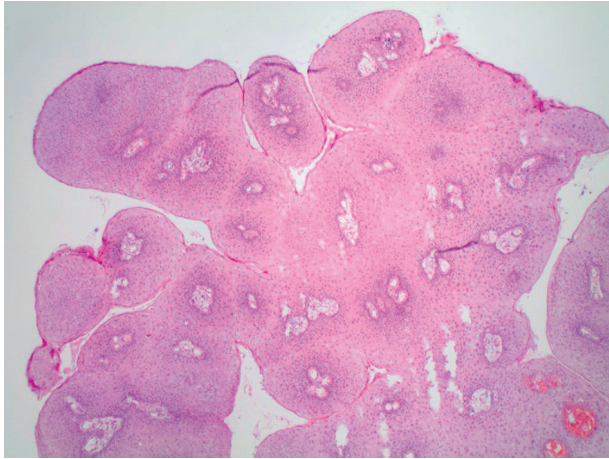


Fig. 3. Papilloma planoepitheliale. HE, magnification 400×

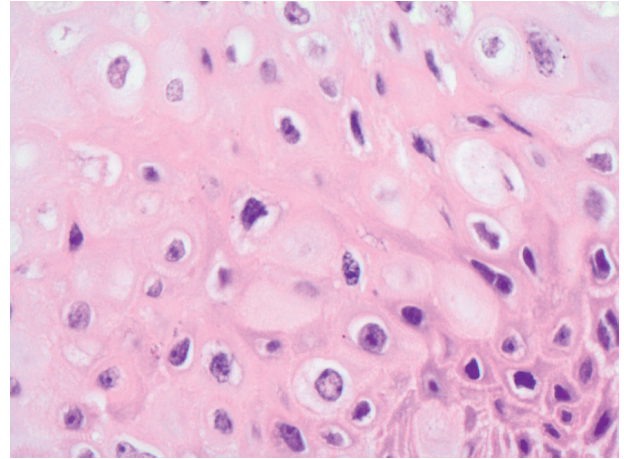


Fig. 4. Papilloma planoepitheliale, HE – features of koilocytosis

rolaryngoscopy and under a microscope. The hypopharyngeal mucous membrane during clinical examination did not raise suspicions of HPV infection. The vocal folds and the mucous membrane of the oesophagus were symmetrical and smooth.

The patient came for a follow-up visit 4 weeks after the procedure and complained that he had a feeling of obstruction when swallowing and also suffered from periodic pain that only responded to non-steroidal anti-inflammatory drugs. Local recurrence in the larynx was found during the follow-up visit. The massive growth occupied the entire larynx: the interarytenoid area, two-thirds of the back section of the vocal folds (bilaterally), both vestibular folds, and the oesophageal entrance. As a result, the patient was considered a candidate for a second procedure to remove the lesions with a CO₂ laser. Adjoining areas of inflamed mucous membrane were also vaporised during the procedure, due to suspected infiltration.

After the next 3 months, during which 2 tumour removal procedures were conducted, the patient returned to the hospital complaining of increasing pain and difficulty in swallowing. The patient could only ingest liquid and pulped food. Because the patient presented increasing difficulty breathing which impeded efforts to insert a laryngeal tube into the trachea during intubation, a lower tracheotomy was performed. At the time, a pedunculated lesion was removed in a Kleinsasser microlaryngoscopy from the back sections of the vocal cords, the interarytenoid area, and the oesophageal entrance. Oesophagoscopy revealed that the entire length of the oesophageal lumen, up to the cardia, was clear of any pathological infiltration.

The patient again returned 3 weeks later to report increasing pain and a palpable, painful tumour on the neck. Physical examination revealed a slightly movable tumour, 4 cm in diameter, on the left side of the neck, with inflamed, red skin in the area above the tumour. A local tumour covering the glottis and clos-

ing the oesophageal entrance was discovered in the hypopharynx. Imaging studies (CT and MRI of the neck and X-ray of the oesophagus with water solution contrast) revealed extensive tumour masses spreading from the laryngeal pharynx to the upper mediastinum and ending at the level of the aortic arch. This infiltration caused nearly complete lumen occlusion of the laryngeal pharynx, larynx, and oesophagus. In addition, involvement of the thyroid cartilage, the left thyroid lobe, and the cricoid cartilage was discovered. The tumourous mass on the left side of the neck also involved the neck vessels and traversed these vessels into the upper mediastinum. Towards the back, the masses filled the pre-spinal area.

After all of the aforementioned imaging studies had been done, the multidisciplinary team recommended a gastroscopy (using a flexible endoscope). Using an electrocoagulation loop and argon plasma during the gastroscopy, the team removed extensive papillomatous masses from the oesophageal lumen, from the oesophageal mouth to a level 2 cm above the Z line. At the same time, an incision was made to drain a deep abscess in the soft tissues of the neck. As a consequence of the aggressive progression of the disease, the papillomatosis had spread to the soft tissues of the neck.

Initially, we thought that the aggressive nature and quick progression of the lesion was due to congenital or acquired immunodeficiency. A battery of immunological tests from peripheral blood were done. Immunophenotypic analysis of leukocytes revealed a normal absolute count. The relative and absolute counts of basic lymphocyte subsets of T cells, B cells and NK cells were normal for the age. The CD4+/CD8+ T cell ratio was normal. The expression of adhesion molecules CD11a, CD11b, CD11c and CD18 on leukocytes was also normal. Test for HIV was negative. No immunodeficiency was discovered that could cause such atypical, dynamic progression of the disease.

Further endoscopic procedures were ordered. These included a combined laryngoscopy of the pharynx and the larynx with oesophagoscopy and gastroscopy. A CO₂ laser was always used during microlaryngoscopy. An electrocoagulation loop and argon plasma were also repeatedly used during gastroscopy. These procedures were mainly palliative, to ensure that the digestive and respiratory tracts remained open. However, each procedure was more difficult than the previous one due to scars and adhesions. Gastrostomy was required due to the patient's increasing difficulty in swallowing.

After 6 more procedures conducted to remove the papillomatous masses using argon plasma and electrocoagulation during microlaryngoscopy with gastroscopy, it was decided that the patient should be treated with the antiviral drug cidofovir [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine; HPMPC]. The drug was injected directly into the tumour mass. The first injection inhibited disease progression and even led to a partial reduction of the tumour mass. Cidofovir was administered in total 7 times directly into the tumourous mass and 4 times intravenously, with at least a 2-week break between injections. No side effects from the drug usage were observed. Before each injection, the patient was given acetylcysteine to prevent nephrotoxicity, which is a known effect of cidofovir. Kidney function was monitored by testing creatinine clearance with GFR calculation and diuresis monitoring. To rule out kidney damage, total, direct, and indirect bilirubin levels were also checked before and after the drug was administered. Gradually, cidofovir's effect on the lesion began to decrease. Subsequent doses of the drug did not have the desired effect and eventually the tumour started growing again, even with administration of the drug.

After 13 months of administering multimodal treatments without being able to control the disease (despite having consulted European centres that specialised in the treatment of papillomatosis), we decid-

ed to administer palliative radiotherapy (total dose of 2000 CGy/T). The radiotherapy treatment obliterated the tumour's small vessels, thus decreasing the risk of bleeding from the neck tumour. Although radiotherapy is not a standard approach in such cases, we believed it would help to slow the disease progress; however, the disease continued to progress, further weakening the patient and leaving him emaciated. Finally, the patient died in the intensive care unit due to massive bleeding in the upper respiratory tract, 16 months after the initial diagnosis.

Discussion

Recurrent laryngeal papillomatosis is usually restricted to the vocal folds. It has a prevalence rate of 2 per 100,000 adults (according to the National Institute of Deafness and Other Communication Disorders) and 4 per 100,000 children [2, 5]. No prevalence statistics are currently available for Poland. Peak incidence is in the third and fourth decades of life. The childhood form of the disease is usually more aggressive than the adult form. The disease is caused by HPV, most commonly HPV 6 and 11 in the respiratory tract.

Standard treatment of papillomatosis involves surgical removal, usually by CO₂ or Nd:YAG laser. Due to the chronic nature of the disease and the high likelihood of recurrence, 20% of patients require follow-up treatment to control the disease. Current criteria for the need for follow-up treatment include: more than 4 surgical procedures in a year; short recurrence period of respiratory papillomatosis; and dynamic spread of the disease. Local and systemic substances used to treat the disease include: indole-3-carbinol, interferon, acyclovir, ribavirin, retinoic acid, cidofovir, vaccines, zinc, anti-reflux medication and photodynamic therapy [6]. Statistics on the therapeutic efficacy of such treatments are collected by the Recurrent Respiratory Papillomatosis Foundation (Table I).

Table I. Effects of follow-up treatment on efficacy of treatment of recurrent laryngeal papillomatosis. Statistics according to the Recurrent Respiratory Papillomatosis Foundation (RRPF)

TREATMENT	NUMBER OF USERS	NO RESPONSE	IMPROVED	COMPLETE REMISSION	PARTIAL RESPONSE
I3C/DIM	133	61	72	27	45
DIM	7	2	5	1	4
Interferon	61	26	35	5	39
Acyclovir	31	20	11	4	7
PDT	19	13	6	1	5
Retinoid	16	10	6	0	6
Mumps	15	6	9	3	6
Cidofovir	20	2	18	4	14

I3C – indole-3-carbinol; DIM – diindolylmethane; PDT – photodynamic therapy

The most commonly used drug to complement surgical treatment is interferon alfa. Leventhal *et al.* reported that extended administration of interferon (up to 18 months) has a relatively high therapeutic efficacy: 47 out of 60 patients (78%) in that study had either a complete remission (22 patients) or a partial response (25 patients) [7]. However, if the disease has spread to the lungs and other organs, interferon treatment seems to be less effective. The advanced stage of the disease in our patient, when the infiltration had spread to the larynx, the oesophagus, the thyroid, the soft tissues of the neck and the upper mediastinum, indicated that the efficacy of interferon would be limited. The most recent anti-viral drug used to treat papillomatosis is cidofovir. Its treatment efficacy can be as high as 80% (according to RRP; see Table I). Due to the risk of nephro- and hepatotoxicity (according to Sajan *et al.* [8]), the treatment is recommended for patients with a history of severe and resistant disease. The efficacy of cidofovir and its side effects have been discussed in Europe for some time. The drug is registered for the treatment of retinal inflammation caused by cytomegalovirus (CMV) in patients with acquired immune deficiency syndrome (AIDS). However, it is also commonly used off-label to treat respiratory papillomatosis in adults and children, with significant therapeutic success, as numerous papers have shown. In our case, the efficacy of cidofovir appeared to be limited: it temporarily restricted the dynamic development of the disease, but only until a certain stage. According to Derkay [9], despite the reservations of pharmaceutical companies concerning the drug's toxicity and oncogenic potential, it seems to be effective in controlling the development of respiratory papillomatosis. The latest reports indicate that cidofovir administration does not appear to induce previously suspected dysplastic lesions in HPV-infected epithelium [9]. In our patient, multiple samplings of the tumour mass and normal mucous membrane did not reveal the presence of neoplasm or epithelial dysplasia. Despite the aggressive development of the disease, which did not respond to any treatment, no neoplasm or even dysplasia was ever found.

Neoplastic transformation occurs rarely and is mostly observed in the case of pulmonary papillomatosis. The prevalence rate of neoplastic transformation in adults is 3-7% [10]. Predisposing factors for the development of cancer (according to Vambutas *et al.*) are smoking, radiotherapy and other factors that damage DNA. None of these factors were present in our patient.

The chronic nature of the disease, along with multiple recurrences, can lead to dissemination from the larynx to the tracheal lumen, or even to the bronchial system and the lungs. Many authors indicate that tracheotomy contributes to disease spread. The aggres-

sive progression of the disease in our case led to significant narrowing of the laryngeal and tracheal lumen, resulting in acute dyspnoea; as a result, we had to perform a tracheotomy to open the respiratory tract.

We elected to administer palliative radiotherapy in order to treat repeated episodes of bleeding caused by the neck tumour (which also invaded the area of the tracheostomy) and due to the lack of alternative treatments. There is no information in the literature about the use of radiotherapy to treat laryngeal or pulmonary papillomatosis. We used it to obliterate the pathological blood vessels of the tumour in order to lower the risk of bleeding. The treatment decreased the perfusion of the tumours, but did not lead to a remission.

In the literature, case studies of dynamic development of respiratory papillomatosis have been reported previously. Katsenos and Becker (the Department of Interdisciplinary Endoscopy, Thoraxklinik at Heidelberg University, Heidelberg, Germany) described two cases, one of which ended in the death of a patient [11]. The patient had several years of history of laryngeal papillomatosis, with childhood onset of the disease. The advanced disease process affected the larynx, trachea, and the upper lobe of the right lung. HPV type 6 was found. The patient was diagnosed with squamous cell carcinoma of the lung. Radiotherapy and removal of the tumour from the right lung did not have the desired therapeutic effect, and the patient died in the post-operative period. In the case discussed in this paper, the patient did not have any other concurrent diseases. Despite extensive diagnostic testing, we were unable to find any neoplastic disease. Papillomatosis was the only disease, and its aggressive development led to the patient's death.

Conclusions

Laryngeal papillomatosis is a chronic disease in which recurrences are common. As a result, patients often must undergo frequent interventions, which negatively impact their quality of life. The current treatment of choice for papillomatosis is laser ablation. In the case of aggressive, uncontrolled progression – when the infiltration spreads beyond the larynx and the hypopharynx – there are no alternative treatment methods that would lead to an effective cure.

The authors declare no conflict of interest.

References

1. Silver RD, Rimell FL, Adams GL, et al. Diagnosis and management of pulmonary metastasis from recurrent respiratory papillomatosis. *Otolaryngol Head Neck Surg* 2003; 129: 622-629.
2. Goon P, Sonnex C, Jani P, et al. Recurrent respiratory papillomatosis: an overview of current thinking and treatment. *Eur Arch Otorhinolaryngol* 2008; 265: 147-151.

3. Rehberg E, Kleinsasser O. Malignant transformation in non-irradiated juvenile laryngeal papillomatosis. *Eur Arch Otorhinolaryngol* 1999; 256: 450-454.
4. Van Cutsem E, Snoeck R, Van Ranst M, et al. Successful treatment of a squamous papilloma of the hypopharynx-esophagus by local injections of (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine. *J Med Virol* 1995; 45: 230-235.
5. Reeves WC, Ruperelia SS, Swanson KI, et al. National registry for juvenile-onset recurrent respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg* 2003; 129: 976-982.
6. Gallagher TQ, Derkay CS. Pharmacotherapy of recurrent respiratory papillomatosis: an expert opinion. *Expert Opin Pharmacother* 2009; 10: 645-655.
7. Leventhal BG, Kashima HK, Mounts P. Long-term response of recurrent respiratory papillomatosis to treatment with lymphoblastoid interferon-alfa-N1. Papilloma study Group. *N Engl J Med* 1991; 325: 613-617.
8. Sajan JA, Kerschner JE, Merati AL, et al. Prevalence of dysplasia in juvenile-onset recurrent respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg* 2010; 136: 7-11.
9. Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. *Laryngoscope* 2008; 118: 1236-1247.
10. Donne AJ, Hampson L, Homer JJ, Hampson IN. The role of HPV type in recurrent respiratory papillomatosis. *Int J Pediatr Otorhinolaryngol* 2010; 74: 7-14.
11. Katsenos S, Becker HD. Recurrent respiratory papillomatosis: a rare chronic disease, difficult to treat, with potential to lung cancer transformation: apropos of two cases and a brief literature review. *Case Rep Oncol* 2011; 4: 162-171.

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