Case Report

Successful Use of Intralesional and Intravenous Cidofovir in Association With Indole-3-Carbinol in an 8-Year-Old Girl With Pulmonary Papillomatosis

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We report the history of an 8-year-old girl who was treated for suspected lung lesions of respiratory papillomatosis with Indole-3-Carbinol, local and intravenous injections of Cidofovir for 27 months. This is the first report where a complete cure of the lung lesions occurred in a child, and was sustained for at least 24 months.

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scarring. When the child needs more than four surgical interventions per year, adjuvant therapies are considered (α -interferon, photodynamic therapy, indole-3-carbinol, and antiviral drugs including Cidofovir) [Derkay, 2001]. Intralesional injections of Cidofovir have been used with success since 1993 [Van Cutsem et al., 1995]. More recently, some case reports have suggested the usefulness of systemic Cidofovir in the treatment of severe recurrent respiratory papillomatosis in adults [Dancey et al., 2000; Armbruster et al., 2001] and children [Van Valckenborgh et al., 2001].

We report the history of an 8-year-old girl who received 37 cures of intravenous (i.v.) Cidofovir in association with local injections and Indole-3-Carbinol for the treatment of disseminated pulmonary papillomatosis.

INTRODUCTION

Laryngeal papillomatosis or recurrent respiratory papillomatosis is the most common tumor of the upper respiratory tract in children and is due to an infection with a human papillomavirus (HPV), a member of the Papillomaviridae family [Derkay, 2001]. Even if the lesion is generally benign histologically, its resistance to therapy leads to frequent recurrences with a potential for obstruction of the upper respiratory tract. Some complications may occur with a poor prognosis such as, malignant conversion or extension to the lower respiratory tract with ensuing lung failure [Gabbott et al., 1997; Derkay, 2001]. In the juvenile onset type, usually acquired perinatally, diagnosis is made at 2–4 years of age—the early age diagnosis being a risk factor for severe disease [Gabbott et al., 1997]. Children with aggressive respiratory papillomatosis need many surgical procedures and are at high risk of iatrogenic morbidity. The first line treatment is based on endoscopic excision of the lesions to avoid tracheotomy. CO₂ laser combined with operating microscope and a no-touch technique is thought to minimize damage to the upper respiratory tract and vocal cords, and to limit

CASE REPORT

A-C.S was a 34-month-old girl when she was diagnosed with recurrent respiratory papillomatosis. Symptoms had begun 28 months earlier with recurrent upper respiratory tract infections. Her history was, otherwise, unremarkable. Between diagnosis in September 1994 and November 1997 (Fig. 1), she underwent 25 procedures of CO₂ laser vaporization and two trials of subcutaneous interferon γ (up to 300.000 UI/kg/day for 5 and 9 months, respectively). Local injections of Cidofovir were then started (32 procedures between November 97 and May 2000, 21 of which were associated with CO₂ laser vaporizations – mean: 1/1.5 months). During the course of her disease, the following complications

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Fig. 1. Timetable showing occurrence of complications and treatments given. i.v., intravenous; RRP, recurrent respiratory papillomatosis; IFN, interferon.

were noted (Fig. 1): severe scarring causing glottic stenosis, later leading to reconstructive surgery; two episodes of pneumonia; two episodes of glottis oedema, one of which required intubation and 24 hr mechanical ventilation; a subcutaneous and mediastinal emphysema requiring tracheostomy (for 10 days) and a pneumomediastinum requiring high concentrations of oxygen for 24 hr. A control computed tomography (CT) scan of the thorax performed in March 2000 showed circular lesions of the right upper lobe (Fig. 2), suggesting extension of the disease in the thorax. Clinical examination was normal except for severe hoarseness and a mild degree of upper respiratory tract obstruction. Her weight was 31.0 kg and her height 134 cm. Oxygen saturation was normal and her lung function showed an increased resistance both by oscillation and by the interrupter technique, and there was no reversibility after bronchodilator inhalation. She was started on weekly injections of 5 mg/kg of i.v. Cidofovir (Vistide®), according to the prescribed protocol [Van Valckenborgh et al., 2001]. Injections were preceded by 24 hr hyperhydration and associated with probenecid (25 mg/kg then 10 mg/kg/6 hr for 24 hr). Indole-3-Carbinol (200 mg/day) was installed at the same time. During a 27 month period (Fig. 1), she received 37 courses of i.v. Cidofovir, associated with 37 local injections (and 15 sessions of

CO₂ laser – mean: 1/1.8 months). Renal function parameters were checked each time as was the blood cell count. The treatment was well tolerated, with no gastrointestinal side effects and the renal function remained normal (proteinuria <4 mg/kg/hr, creatinine clearance 83–120 ml/min/1.73 m²). She developed some cutaneous

Fig. 2. CT scan of the chest revealing two nodules in the right upper lobe probably due to pulmonary extension of respiratory papillomatosis.

lesions, probably due to probenecid but these lesions were well controlled with antihistamines. Concentrations of Cidofovir in serum, taken 1 hr after intravenous infusions, were constant over the 27-month treatment period ($15.0 \pm 3.7 \mu\text{g/ml}$; $n = 27$). The urinary recovery of Cidofovir over 24 hr after infusion was $101.9 \pm 19.1\%$ of the total dose injected ($n = 25$).

Control scans were performed after 4 doses (extension of the lesions to the left upper lobe and right lower lobe), 11 doses (regression of the previously described lesions, some small new lesions in the left lower lobe), 19 (no lesions), 26 (no lesions), and 36 doses (no lesions). It was then decided to stop the i.v. Cidofovir injections. After 24 months follow-up, a control CT scan failed to show any lung extension of her disease. She was then treated with local injections of Cidofovir, Indole-3-Carbinol, CO₂ laser surgery, and photodynamic therapy was considered.

DISCUSSION

Lung extension is considered as a rare complication of recurrent respiratory papillomatosis (about 1%) and may be precipitated by surgical procedures such as tracheotomy [Derkay, 2001]. As no treatment is available to cure this complication it usually progresses to respiratory failure and death, thus rendering the prognosis very poor [Gabbott et al., 1997; Derkay, 2001]. In this case, a tracheotomy had been performed more than 3 years before the CT scan revealed the lung lesions, and was maintained for 10 days. Diagnosis of pulmonary papillomatosis was considered based on the clinical history and the radiological aspect of the lesions with secondary bilateralization. The lack of pathognomonic cavity and the fact that no biopsy could be advocated because of the small size of the lesions did not allow a certain diagnosis.

Cidofovir is an acyclic nucleoside phosphonate that has proved efficacious both *in vitro* and *in vivo* against HPV-infections and HPV-induced lesions [Snoeck et al., 2001]. Intralesional injections of Cidofovir have been used for about 10 years [Van Cutsem et al., 1995]. As a rule, Cidofovir at a concentration of 2.5 mg/ml was injected directly in the different laryngeal papillomatous lesions during microlaryngoscopy under general anesthesia. All patients had a clearly visible response with a majority (14/17 in the original study) [Van Cutsem et al., 1995] demonstrating a complete disappearance of the lesions. No inflammation, scarring, fibrosis, nor systemic toxicity were noted. These results have been largely confirmed [Pransky et al., 1999; Snoeck et al., 2001]. In our case, local injections allowed a complete disappearance of the supraglottic, but not the tracheal, lesions. We believe that the tracheal lesions were not cured by local injections since they were more difficult to reach with the glottic reshaping.

More recently, some authors have reported the successful use of i.v. Cidofovir in adults with severe RRP. Dancey et al. [2000] have reported the successful combination of subcutaneous interferon- α -2a and i.v.

Cidofovir in a 35-year-old woman with bilateral multiple pulmonary nodules and cysts. She received 51 doses of Cidofovir (5 mg/kg) associated with probenecid. Probenecid had to be discontinued due to anaphylactic reactions. Armbruster et al. [2001] similarly described their experience with the combination of i.v. Cidofovir and interferon- α -2b in a 34-year-old woman with bilateral round cavitating consolidations due to recurrent respiratory papillomatosis. The only case report involving a child was an 8-year-old Chinese girl [Van Valckenborgh et al., 2001] who showed significant regression of lung lesions and no side effects after 23 doses of i.v. Cidofovir (5 mg/kg). She did not reappear for follow-up.

Thus, this is the first report where a complete disappearance of lung lesions occurred when using systemic Cidofovir in association with local injections and Indole-3-Carbinol in a child, and the response was sustained for at least 24 months.

Indole-3-Carbinol has been used as an adjuvant therapy but has never been associated with a complete cure of lung lesions of respiratory papillomatosis. Thus, we believe that the cure observed in this case was essentially due to the adjunction of i.v. Cidofovir.

The tracheal lesions were also controlled more easily. During the 3 months preceding intravenous treatment, recurrent dyspnea associated with tracheal obstructive lesions imposed a surgical intervention every 3 weeks but when intravenous treatment was started, it seemed to stunt the tumoral growth leading to less frequent CO₂ laser vaporizations (every 6 weeks), thereby reducing the risk of postoperative complications. After the treatment was stopped, she needed again more frequent surgical interventions leading us to consider photodynamic therapy.

Up to 100% of the Cidofovir is recovered in the urine, its renal clearance being somewhat reduced by probenecid that blocks active renal tubular secretion of the drug [Cundy, 1999]. The main toxicity is a dose-related proteinuria and creatinine elevation. To reduce the risk of these renal side-effects, hyperhydration and concomitant administration of probenecid have been advocated [Snoeck et al., 2001]. However, probenecid has its own toxicity, which may lead to therapy discontinuation.

In this case, plasmatic concentrations of Cidofovir (C_{max} values) were within the range of those expected for a 5 mg/kg intravenous administration in adults [Cundy, 1999] and urinary recovery showed a normal elimination pattern. Unpublished data from this team have shown that local injections with this protocol do not modify the pharmacokinetic profile of Cidofovir. Thus, our data do not support renal accumulation of the drug even after repeated and long-term administration. No disturbance of the renal function was noted.

In conclusion, systemic and local Cidofovir, in association with Indole-3-Carbinol, seems to be a promising treatment for patients with pulmonary extension of respiratory papillomatosis, since it may lead to complete regression of the lung lesions. Tracheal involvement

is also more easily controlled though, not completely cured. Provided hyperhydration and probenecid are associated, and renal function is monitored, this treatment seems safe. A longer follow-up may be necessary to assess (the lack of) recurrence.

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