Methemoglobin is unable to transport and unload oxygen in the tissues, effectively reducing the amount of available hemoglobin in the body for oxygen transport. Methemoglobin levels up to 25% can be well tolerated in otherwise healthy patients, but levels >50% are life threatening. High levels of methemoglobin cause a dark brown (chocolate) discoloration of blood, and patients appear cyanotic. Methylen blue, an electron donor, repletes the endogenous cellular antioxidant systems. Its effect is evident in minutes, and the effect lasts for up to 90 min. High doses (7 mg/kg) of methylene blue or its use in patients with glucose-6-phosphate deficiency can precipitate methemoglobinemia; it therefore needs to be used with caution.

Ifosfamide is an alkylating chemotherapeutic agent that is used in the treatment of testicular, lung, breast, cervical, ovarian cancers, and sarcomas. The parent compound can be administered IV or po, but it requires transformation to 4-hydroxy-ifosfamide by the cytochrome P450 enzymes of the liver. In tumor cells, this compound is transformed to the active cytotoxic metabolites ifosfamide mustard and acrolein as well as carboxyifosfamide, 4-ketoifosfamide, and 4-thioifosfamide (Fig 1). The latter compound reacts with glutathione and can deplete cell antioxidant stores. Some of the parent compound is converted to chloroethylifosfamide and chloroacetaldehyde, which also react with glutathione. Ifosfamide has been shown to induce its own metabolism after administration of one dose (autoinduction).

Our patient was receiving phenobarbital, a potent inducer of the cytochrome P450 enzymes, and probably metabolized ifosfamide faster than expected. On the second day, ifosfamide autoinduction further increased its rate of metabolism, causing increased amounts of ifosfamide metabolites, which in turn reduced glutathione stores in RBCs. This caused overt methemoglobinemia leading to respiratory distress. Mesna, when used with ifosfamide, protects the urinary system, but not the RBCs, and therefore did not adequately prevent the depletion of the cellular reducing systems of the RBCs. The prompt reversal with only one dose of methylene blue suggests that the offending agent had been removed. An extensive review of the literature did not reveal an obvious mechanism for adriamycin or dacarbazine to cause methemoglobinemia, nor did it show any reported cases. Cyclophosphamide, a compound related to ifosfamide in structure and metabolism, is reported to cause methemoglobinemia.

Physicians need to have high clinical suspicion for methemoglobinemia in patients with cyanosis, respiratory symptoms out of proportion to their blood gas, equivocal oximetry, and use of new medications or medications known to cause methemoglobinemia. Our report suggests that ifosfamide should be added to the list of drugs causing methemoglobinemia and offers a potential mechanism for ifosfamide-induced methemoglobinemia. Physicians using ifosfamide should be aware of this potentially life-threatening reaction, especially in patients who are receiving agents that induce the cytochrome P450 system.

References

Successful Treatment of Juvenile Laryngeal Papillomatosis-Related Multicystic Lung Disease With Cidofovir*

Case Report and Review of the Literature

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Cidofovir, a nucleoside analog antiviral agent, has been used with moderate success in the treatment of juvenile laryngeal papillomatosis (JLP) by direct intralesional injection. We report the first case where IV cidofovir was used successfully to treat a rare but lethal multicytic lung disease complicating JLP. A 35-year-old woman with a history of JLP requiring multiple laser ablations of laryngeal papillomata each year presented with hemoptysis and was found on CT scan to have bilateral, multiple pulmonary nodules and cysts. The results of BAL fluid analysis demonstrated no evidence of malignancy, and cultures were negative for fungi and mycobacteria. Molecular DNA typing of a biopsy specimen ob-

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tained from a laryngeal papilloma confirmed infection with human papilloma virus type 11. She received 12 months of treatment with IV cidofovir followed by 9 months of combined treatment with IV cidofovir and subcutaneous interferon-α-2A. This therapeutic regime resulted in a markedly decreased requirement for surgical removal of laryngeal papillomata, and CT scanning documented the regression of the lesions in the lung parenchyma that persisted after the discontinuation of therapy. The results of this case demonstrate that cidofovir may be used successfully to treat JLP-related lung disease and suggest that further studies are warranted.

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Key words: cidofovir; human papilloma virus; interferon; juvenile laryngeal papillomatosis

Abbreviations: HPV = human papilloma virus; JLP = juvenile laryngeal papillomatosis

Laryngeal papillomatosis, a condition characterized by a relapsing, benign, epithelial neoplastic polyps in the larynx, is caused by infection with the human papillomavirus (HPV).1 In the United States, the juvenile-onset form of the disease (juvenile laryngeal papillomatosis [JLP]) is diagnosed in 1,500 children each year.2 JLP usually resolves at puberty but can persist into adulthood.3 Although the condition is usually limited to the larynx, it involves the tracheobronchial tree in 2 to 5% of cases and the lung parenchyma in 1% of cases.4

Since the first report in 1932 of lung parenchymal disease complicating JLP, there have been a total of 16 cases reported in the English language literature.1,4–18 In six of the cases, the patients had died at the time of the report. Five additional cases are not included because of the presence of lung cancer, which made conclusions about JLP-related parenchymal disease difficult to reach.10,19–21 Treatment of the lung complications has varied considerably but has generally been unsuccessful. Despite the knowledge that the disease is a result of an infection with HPV, until recently antiviral drugs have not been used.

Nucleoside analog antiviral medications, such as acyclovir and ganciclovir, are standard treatments for infections with herpes simplex, varicella zoster, and cytomegalovirus.22–24 A newer generation of nucleoside analog cidofovir (Pharmacia & Upjohn; Mississauga, ON, Canada), has been reported to be successful in treating HPV in patients with esophageal or anal lesions.25,26 In addition, Snoek et al.27 have reported success using intralesional injections of cidofovir to treat 17 patients with severe, local JLP. We report a case of lung parenchymal disease complicating JLP that was successfully treated with IV cidofovir.

Case Report

A 35-year-old woman with a history of laryngeal papillomatosis since infancy was evaluated for hemoptysis and progressive dyspnea on exertion. Three weeks prior to referral, she had an episode of retrosternal chest pain and shaking chills that lasted for 8 h. One week later, she developed daily episodes of hemoptysis and progressively worsening dyspnea.

Since infancy, she had been treated for laryngeal papillomatosis with multiple laryngoscopic resections and, more recently, with laser ablation. At the time of referral, she had had a total of 96 resections and laser ablations, with 4 laser treatments in the preceding year.

A physical examination revealed a woman with a hoarse voice and audible wheeze who was not in respiratory distress. Her vital signs were normal, and she had no evidence of lymphadenopathy, clubbing, peripheral cyanosis, hepatosplenomegaly, rash, or active arthritis. A chest examination was remarkable for faint wheezes on both inspiration and expiration, which were loudest at the neck.

Laryngoscopy demonstrated multiple laryngeal papillomata, and laser ablation was performed with the resolution of her dyspnea. A high-resolution CT scan of the thorax (Fig 1) demonstrated multiple, bilateral nodules and thin-walled cysts, with the largest cyst measuring 2 cm in maximum dimension. Fiberoptic bronchoscopy was performed under a local anesthetic. Neither mucosal abnormalities nor the source of hemoptysis was identified.

Four months later, the patient required another laser treatment for the recurrence of her laryngeal disease. Rigid bronchoscopy was performed at the time, with excellent visualization of the trachea, right and left mainstem bronchi, and bronchus intermedius. Although several laryngeal papillomas were obvious, no endobronchial lesions were seen. HPV type 11 was identified in a sample of the resected papilloma. A lung biopsy was recommended, but the patient declined. A presumptive diagnosis of HPV-related multicystic lung disease was made. She was followed with serial high-resolution CT scans of her thorax.

Because of increasing pulmonary parenchymal nodules and cysts, antiviral treatment was considered.

Treatment with cidofovir (Vistide; Gilead Sciences; Foster City, CA) was begun at a dose of 5 mg/kg administered every 2 weeks in conjunction with probenecid in order to diminish nephrotoxicity. The patient’s CBC count and differential count, serum creatinine levels, and urinalysis results were monitored weekly. Two months after treatment was begun, she had an anaphylactic reaction to probenecid, which was discontinued. She continued to receive cidofovir, receiving aggressive hydration (6 L IV saline solution before treatment and 3 L oral hydration after treatment) to prevent nephrotoxicity. Following 12 months of treatment, a CT scan of the thorax demonstrated regression of the pulmonary parenchymal nodules and cysts (Fig 1). In addition, her need for laser polypectomy decreased considerably; only two laser treatments were required in the year during treatment compared with five and four in each of the two preceding years.

Following 12 months of treatment with cidofovir, interferon-α-2A was added as an immune-enhancing agent in anticipation of the cessation of cidofovir therapy. The initial dose was 3 million units subcutaneously daily for 1 month, which then was reduced to 3 million units three times weekly. Four months later, partial alopecia and leukopenia developed, requiring a dose reduction of both agents. Interferon-α-2A therapy was stopped after a total of 9 months of treatment. Cidofovir was continued at a dose of 4 mg/kg every 2 weeks for an additional 12 weeks and then was stopped after the patient had received a total of 51 doses.

At present, 18 months after the cessation of all therapy, she continues to do well and has required laser polypectomy only once. Pulmonary function testing shows normal lung volumes, diffusion capacity, and airflow, including a maximum inspiratory flow at 50% of vital capacity of 3.66 L (232% of predicted). The most recent CT scan of the thorax demonstrated a stabilization of her parenchymal disease after a total of 24 months of therapy.
Although rare, extralaryngeal disease in patients with JLP does occur and portends a poor prognosis. Clinical clues may include fever, hemoptysis, sputum production, or progressive dyspnea despite control of the laryngeal disease. Only one case of lower respiratory tract involvement has been reported in the absence of laryngeal disease. Bronchoscopy may demonstrate lesions throughout the tracheobronchial tree, suggesting possible parenchymal lung involvement. Chest radiographs have shown persistent postobstructive atelectasis, recurrent airspace consolidation, recurrent pneumothoraces, and nodules with and without cavitation. Chest CT scans have demonstrated multiple nodules, with or without cavitation, as well as thin-walled cysts.

Despite moderate success using interferon-α-2A to treat JLP that is limited to the larynx, attempts to treat lung involvement have been largely empiric and unsuccessful. In all cases, the pathology of the biopsy or autopsy specimens has been identical to that of the laryngeal lesions. Antibiotics, surgery, autogenous vaccine, transfer factor, and chemotherapy, including cyclophosphamide, methotrexate, bleomycin, and interferon, have been tried without success.

It has been only in the last 2 to 3 years that antiviral drugs have been used to treat this disease. In the early 1980s, molecular diagnostic technology enabled the identification of HPV as the etiologic agent of JLP. HPV type 6 appears to be most commonly associated with extralaryngeal involvement. Despite this knowledge, the first report of the use of antiviral agents to treat JLP was published in 1998.

Cidofovir (also known as HPMPC, GS-0504, and 1-[(S)-3-hydroxy-2-(phosphonomethoxy)propyl]cytosine dihydrate) is a cytosine nucleoside analog that has been shown both in vitro and in vivo to be active against the

Figure 1. High-resolution CT scan images of the thorax demonstrating multiple nodular and cystic lesions (top, A) prior to treatment with cidofovir and (bottom, B) following 12 months of treatment. Note the regression in the nodular and cystic lesions.
Herpesvirus group. The main indication for its use has been in suppressing cytomegalovirus retinitis complicating AIDS. The dose-limiting toxicity of cidofovir is renal failure from acute tubular necrosis. This condition was observed in AIDS patients at doses of 3 and 5 mg/kg given once weekly for 2 weeks then biweekly but was prevented using probenecid and hydration prior to each dose. Reversible neutropenia was the next most common adverse effect seen.

Two case reports on the use of cidofovir against HPV in humans were published in 1995. In one case, local injections of the drug into a squamous papilloma of the hypopharynx-esophagus successfully eradicated the lesion. In the second case, three patients with AIDS and relapsing anal warts received cidofovir topically with complete resolution of the warts. No significant adverse effects were noted. Most recently, intraläsional injections of cidofovir were used to successfully treat 17 patients with severe, localized JLP.

During the 24 months of treatment with cidofovir, our patient demonstrated a markedly diminished requirement for laser polypectomies, and serial CT scans demonstrated the regression and then the stabilization of the parenchymal nodules and cysts (Fig 1). The pulmonary parenchymal lesions have not progressed despite the discontinuation of all antiviral therapy, and the patient has not required a laser polypectomy for the 18 months since treatment was stopped, suggesting that the effects of cidofovir have persisted long after the discontinuation of the medication.

CONCLUSION
To our knowledge, this is the first report of the use of systemic cidofovir for treating parenchymal lung disease complicating JLP. Because it is such a rare complication of JLP, it is unlikely there will be an opportunity for a randomized, controlled trial to properly evaluate the efficacy of cidofovir in treating HPV-related multicystic lung disease. However, given the success in eradicating other forms of HPV infection with intralesional injections, it is reasonable to assume that lung lesions would respond similarly. In principal, bronchoscopic or CT-guided injections of cidofovir could be used to treat symptomatic parenchymal lesions, avoiding the systemic toxicities of the drug. Nevertheless, larger, randomized studies are needed to confirm the efficacy of cidofovir therapy in patients with JLP. Aggressive treatment of the disease at its onset may successfully prevent its complications.

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Gastroesophageal Reflux as a Reversible Cause of Allograft Dysfunction After Lung Transplantation*

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Gastroesophageal reflux (GER) is increasingly recognized as contributing to a number of pulmonary disorders. The relationship of GER to pulmonary allograft dysfunction after lung transplantation is unknown. In this report, we describe a lung transplant recipient who developed an acute decline in pulmonary function several months after a retransplantation for chronic rejection. A pulmonary workup at that time, including bronchoscopy with biopsy, revealed bronchial inflammation with no allograft rejection or infection. Because of increasing GI symptoms after retransplantation, the patient also underwent additional testing, which revealed severe acid reflux. The treatment of this patient’s acid reflux with Nissen fundoplication surgery resulted in a prompt and sustained improvement in his pulmonary function. We suggest that GER should be considered among the potential causes of allograft dysfunction after lung transplantation.

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Key words: bronchiolitis obliterans syndrome; gastroesophageal reflux; lung transplantation

Abbreviations: BOS = bronchiolitis obliterans syndrome; CMV = cytomegalovirus; GER = gastroesophageal reflux; OB = obliterative bronchiolitis

Lung transplantation has emerged as a viable therapeutic option for patients with a variety of end-stage pulmonary diseases.1 As immediate posttransplant surgical outcomes have improved and patients are living longer, GI complications are increasingly recognized to occur after lung transplantation.2 In this report, we describe a posttransplant patient who developed severe gastroesophageal reflux (GER) and deterioration of his pulmonary function. The decline in pulmonary function improved dramatically after antireflux surgery. To our knowledge, this is the first case to implicate GER as a reversible cause of allograft dysfunction in a lung transplant recipient.

Case Report

A 23-year-old man underwent a bilateral lung retransplantation in March 1997. The patient originally underwent lung transplantation for cystic fibrosis in January 1995. At the time of the first transplant, he received maintenance immunosuppression with cyclosporine, azathioprine, and prednisone. He also received prophylactic ganciclovir and cytomegalovirus (CMV) Ig because of his CMV mismatch status (donor-positive/recipient-negative) and trimethoprim-sulfamethoxazole for Pneumocystis carinii prophylaxis. The patient did well after the initial transplant surgery but experienced several episodes of mild allograft rejection and one episode of moderate acute allograft rejection within the first posttransplant year. Although each episode of acute rejection responded appropriately to bolus corticosteroids, the patient’s pulmonary function began to decline approximately 15 months after transplantation, which is consistent with a diagnosis of bronchiolitis obliterans syndrome (BOS). Bronchoscopy with biopsy at that time revealed moderate bronchial inflammation, but there was no evidence of acute rejection or infection. Despite augmented immunosuppression with tacrolimus and mycophenolate mofetil, the patient experienced a rapidly progressive decline in pulmonary function and, ultimately, underwent bilateral retransplantation for progressive allograft failure. The patient never complained of any symptoms of regurgitation or acid reflux after the first transplantation.

The patient tolerated the repeat transplantation well and was discharged on the seventh postoperative day. His immunosuppressive regimen included tacrolimus, mycophenolate, and prednisone (initially, at a dose of 20 mg/d). He was treated also with ganciclovir and trimethoprim-sulfamethoxazole prophylaxis and received ranitidine for stress ulcer prophylaxis. A histologic examination of the original transplanted lungs revealed obliterative bronchiolitis (OB). The results of bacterial, fungal, and mycobacterial cultures and CMV immunostains performed on

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