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Case report

[Translated article] Treatment of juvenile recurrent respiratory papillomatosis in a pediatric lung transplant recipient

Tratamiento de la papilomatosis recurrente respiratoria juvenil en un paciente pediátrico receptor de trasplante pulmonar

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Introduction

Juvenile recurrent respiratory papillomatosis (JRRP) typically arises from a chronic infection with the human papilloma virus (HPV) in the respiratory epithelium, which leads to the formation of papillomas. It is usually caused by HPV-6 or HPV-11 and tends to affect the larynx. Despite being a rare condition, it is the most common benign proliferative lesion of the respiratory epithelium in children and exerts a significant impact on their quality of life. It is mainly acquired through vertical transmission, with mean age at diagnosis being 5 years.[1–4]

Given HPV's ability to remain latent in the respiratory epithelium, recurrence of the condition is fairly common and its prognosis unpredictable. Despite its usually benign nature, the disease may exhibit an aggressive course and even lead to the patient's death. Early onset of JRRP and HPV-11 are associated with greater aggressiveness and a poorer prognosis.[1,3–5]

Initial treatment is usually based on surgical resection of the papillomas. However, this is seldom enough, with removal of the latent HPV by means of adjuvant therapy being often required. Currently, no well-defined recommendations exist on such adjuvant therapies, with intralesional (IL) cidofovir and IL or intravenous (IV) bevacizumab being the most commonly used agents.[1–6]

Bevacizumab is a commonly used adjuvant therapy as it inhibits angiogenesis and the development of HPV, papillomas being associated with an overexpression of the vascular endothelial growth factor (VEGF). Because of this angiogenic effect, administration of bevacizumab may result in delayed healing.[2,3,6] Moreover, given that patients with JRRP have been found to exhibit an overexpression of the epidermal growth factor receptor (EGFR) and of cyclooxygenase-2 (COX-2), a combination of erlotinib and celecoxib has been suggested as a therapeutic alternative.[2,4,7,8]

The present report is the first one to describe the case of a lung transplant recipient with JRRP and the second one of a pediatric subject receiving erlotinib and celecoxib as treatment for JRRP.

Case description

This report describes the case of a male patient diagnosed with JRRP (HPV-6) at the age of 15 months. Despite multiple surgeries and adjuvant therapies, including IL cidofovir, the disease did not resolve. At the age of 5, the patient received IV bevacizumab, which elicited a favorable response but had to be withdrawn at 1 year due to proteinuria. When he was 7 years old, a worsening of the patient's respiratory symptoms led to the reintroduction of IV bevacizumab with a satisfactory response and good tolerance. At age 12, the patient developed chronic respiratory insufficiency secondary to the sequelae of pulmonary dissemination of the JRRP, with destruction of the lung parenchyma. As a result, after extensive discussion by the multidisciplinary care team and following careful consideration of all the potential risks, the patient was placed on the lung transplant list. Given the risk of delayed healing following transplantation, IV bevacizumab was suspended (day 0) and replaced by IL bevacizumab at the level of the larynx. A surgical resection was performed and oral therapy with erlotinib (150 mg/day) and celecoxib (200 mg/12 h) was instituted (Fig. 1).

At 5 weeks from initiation of erlotinib and celecoxib, the patient developed moderate renal dysfunction. This prompted a reduction of the dose of celecoxib (200 mg/day), which was withdrawn 5 weeks after initiation of the reduced dose. Four days later, the patient's renal function improved, which allowed reintroduction of full-dose celecoxib, with no adverse events.

Despite a satisfactory initial response, new papillomas were detected in the larynx, the trachea, and the bronchi 5 months after initiation of therapy with erlotinib and celecoxib. A decision was made to

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resume once-monthly IV bevacizumab together with IL bevacizumab and to perform a surgical resection, which resulted in the patient being removed from the transplant list and in the withdrawal of erlotinib and celecoxib. After 2 doses of IV bevacizumab, the patient had a satisfactory evolution, with stabilization of the papillomatosis. This led to the discontinuation of IV bevacizumab and to the maintenance of IL bevacizumab, and of the surgery.

After 1 month, a new worsening of the patient's respiratory symptoms resulted in his inclusion on the transplant list once again. A week later, he underwent a double lung transplant (Fig. 2). Following transplantation, he was started on immunosuppressive treatment with tacrolimus and corticosteroids at a lower-than-usual dose, accompanied by pharmacokinetic monitoring of tacrolimus.

The patient's initial evolution was favorable. However, a month and a half later, new papillomas were identified in the larynx, which led to a surgical resection and initiation of IL bevacizumab. A month later, he developed hoarseness and stridor, which led to the reintroduction of once-monthly IV bevacizumab together with a surgical resection. The clinical course after this was satisfactory, although administration of IV bevacizumab had to be temporarily discontinued due to dehiscence of the sternal suture. Seventeen months after transplantation the patient was still on 1-monthly IV bevacizumab, with an acceptable response and satisfactory evolution, albeit with a recurrence of papillomas in the lungs and in the bronchi.

Fig. 2. Macroscopic appearance of the patient's lung explants.

Discussion

Although PRRJ often exhibits a benign course and is typically confined to the larynx, it may well present with an aggressive evolution. Identification of risk factors is essential to establish the patients' prognosis and institute an effective treatment.[1–5] In the present case, JRRP was classified as severe due to its early onset, the presence of extralaryngeal papillomas and the need for multiple surgeries. Although HPV-11 is the HPV type that has most commonly been linked to aggressiveness, this case demonstrates that HPV-6 may also result in severe JRRP.

Treatment of JRRP is based on surgical resection of the papillomas and on the prevention of recurrence through adjuvant therapy.[1,3–5] In the case presented here, the patient received various adjuvant therapies, but only responded to IV bevacizumab. However, due to his inclusion on the transplant list, and in order to ensure proper healing following surgery, a decision was made to discontinue the treatment. As a result of the lack of response to previous therapies, the patient was initiated on IL bevacizumab and erlotinib with celecoxib.

Several cases of adult patients and one of a pediatric patient have been reported with a favorable response to celecoxib or celecoxib with erlotinib,[9,10] with no clear-cut consensus concerning the agents' role in the context of JRRP.[3] The patient described in this case report exhibited an encouraging initial response but subsequently developed new papillomas. Tolerance was satisfactory, except for the appearance of renal dysfunction of a probably multifactorial origin.

The patient eventually obtained a favorable clinical response with shrinking of the papillomas following a regimen of once-monthly IL and IV bevacizumab. Some authors have suggested spacing out dosing intervals if a favorable response is achieved.

In short, the case discussed here illustrates an instance of aggressive evolution of JRRP that resulted in a lung transplant, as well as the complexities inherent in the pharmacological management of this condition. Optimized pre- and post-transplant adjuvant therapy is required

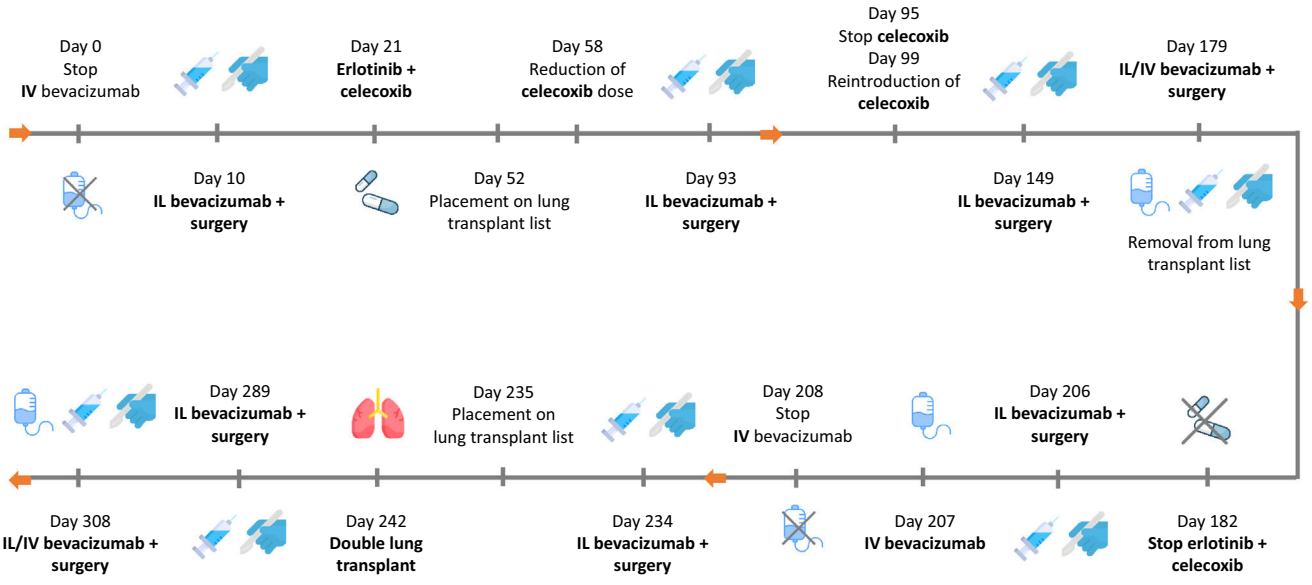

Fig. 1. Flow diagram showing the treatment administered for juvenile recurrent respiratory papillomatosis. HPV: human papilloma virus, IL: intralesional, IV: intravenous.

as well as an intensity of immunosuppression capable of preventing graft rejection but ensuring at the same time adequate control of JRRP. Given that JRRP is associated with such a variable prognosis, it is essential to analyze each case in an individualized way and to carry out studies to establish guidelines that may facilitate the treatment of JRRP, minimizing the impact of the disease on the patients' quality of life and reducing the duration of the therapy.

Informed consent

The legal guardian of the patient provided the required informed consent for the preparation and publication of the manuscript.

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Declaration of competing interest

The authors have declared not to have any conflict of interest with respect to this study.

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