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Review article

Recurrent respiratory papillomatosis: A state-of-the-art review

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ABSTRACT

Recurrent respiratory papillomatosis (RRP) is a benign disease of the upper aero-digestive tract caused by human papillomavirus (HPV) infection, which affects children and young adults. The aim of this review is to describe the main etiological, epidemiological, clinical, diagnostic, and treatment aspects of RRP. Most infections in children occur at birth, during passage through the birth canals of contaminated mothers. In adults, HPV is transmitted sexually. Papillomas usually appear as exophytic nodules, primarily in the larynx, but occasionally involving the nasopharynx, tracheobronchial tree, and pulmonary parenchyma. The disease course is unpredictable, ranging from spontaneous remission to aggressive persistent or recurrent disease. Although it occurs rarely, RRP has the potential for malignant transformation to squamous cell carcinoma. Clinically, RRP usually presents with nonspecific symptoms of airway involvement, including chronic cough, hoarseness, wheezing, voice change, stridor, and chronic dyspnea. Helical computed tomography (CT) is highly accurate for the identification and characterization of focal or diffuse airway narrowing caused by nodular vegetant lesions. The typical CT pattern of lung papillomatosis consists of numerous multilobulated nodular lesions of various sizes, frequently cavitated, scattered throughout the lungs. Bronchoscopy is the most reliable method for the diagnosis of RRP; it enables direct visualization of lesions in the central airways and collection of biopsy samples for histopathological diagnosis, and is also useful for therapeutic planning. The definitive diagnosis of RRP is based on histopathological analysis. Currently, no definitive curative treatment for RRP is available; despite the availability of adjunctive treatments, surgery remains the mainstay of treatment.

Contents

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1. Introduction

Recurrent respiratory papillomatosis (RRP) is generally a benign and self-limited disease, caused by the human papilloma virus (HPV) and characterized by the appearance of papillomatous lesions anywhere in the aero-digestive tract [1–6]. A bimodal age distribution is characteristic, with young children and young adults most commonly affected [1]. The disease is more common in children, and the virus is thought to be transmitted by contact with infected secretions in the birth canal. In adults, HPV infection may occur following oral sex [1–3,7]. The histological presentation is benign squamous epithelial stratification [3]. RRP is typically restricted to the larynx, but it occasionally becomes aggressive, resulting in persistent or recurrent involvement of the nasopharynx, tracheobronchial tree and, more rarely, the pulmonary parenchyma [3,8,9]. The course of the disease is unpredictable, ranging from spontaneous remission to aggressive disease progression, spreading to the lungs and requiring multiple surgical procedures to maintain airway function [6]. A presumptive diagnosis may be made based on medical records and clinical and imaging findings; the final diagnosis is based on histopathological analysis of samples of lesions in the larynx and trachea, collected by bronchoscopy [3].

2. Etiology

HPV is a DNA virus of the Papillomaviridae family with a propensity to infect epithelial cells. It has a non-encapsulated, double-chain icosaedric structure, and is composed of 72 capsomeres approximately 55 nm in diameter [7,10]. Analysis has revealed more than 180 HPV genotypes, with specific affinity for squamous epithelial cells but different tissue preferences, resulting in various clinical manifestations [7]. HPV has etiological associations with many benign and malignant tumors of the epidermal tissues. It is associated strongly with cancer of the cervix and other anogenital tumors, such as carcinoma of the anus, penis, vulva, and vagina, as well as tumors of the head and neck [11].

The subtypes of HPV are classified as being of high and low risk according to their potential for malignant transformation of epithelial cells [1,10]. Subtypes 6 and 11 are responsible for more than 90% of RRP cases [2,7]. Patients infected with type 11 HPV develop more aggressive disease [10], which may lead to significant airway obstruction requiring frequent surgical procedures and adjuvant medical therapies, and sometimes even tracheostomy, to maintain airway patency [2]. Other subtypes, such as 16, 18, 31, and 33, are also associated with RRP, although with lower prevalence [1,2]. Subtypes 16 and 18 are considered to be high risk, with the potential for malignant transformation, particularly to squamous cell carcinoma, which occurs in less than 1% of juvenile RRP cases [3,7,12].

3. Epidemiology

RRP shows a characteristic bimodal distribution, affecting children and young adults [1,6,13]. The juvenile form develops in patients less than 20 years of age [3,5,14]. This form of the disease is generally aggressive, with multiple papillomatous lesions, and has a high recurrence rate [2,3]. The adult form develops after 20 years of age, in the third and fourth decades of life [2,11,14,15], more commonly in men [3]. In this form, the papillomas are often solitary, with a high degree of inflammatory reactivity; they do not usually spread, and recur less frequently than those seen in the juvenile form [3].

The estimated incidence of RRP is approximately 4 per 100,000 in children and 2 per 100,000 in adults [1,2,5,11,13]. The incidences vary according to factors such as age of appearance and socioeconomic status [1]; they are higher in groups with lower socioeconomic status and low educational levels [6]. However, no correlation has been found between socioeconomic status and the severity of the disease [6]. The prevalence of HPV infection has been increasing gradually in the female population. The estimated prevalence in women aged 14–59 is 26.8%, and that in women aged 20–24 years is 45% [6].

HPV infection in children occurs most often at birth, during passage through the birth canals of contaminated mothers [1–3,7,9]. Transmission occurs prior to birth, through the placenta, in about 12% of cases [6]. The presence of maternal anogenital warts during pregnancy is considered to be a primary risk factor for juvenile-onset RRP [7]. The presence of maternal anogenital papillomatous lesions during pregnancy, and particularly during birth, increases the risk of RRP development by about 231 times relative to the absence of such lesions at the time of birth. Approximately 0.7% of infants exposed to maternal anogenital warts develop the disease [6,7,16]. In adults, HPV is transmitted sexually, through oral contact with infected external genitalia [1–3,7]. Sexual activity with multiple partners stands out as a risk factor for HPV infection in adults [7].

4. Pathogenesis

HPV initially infects the basal epithelial layer of the mucous or cutaneous surface through minor excoriation [2]. Subsequently, it activates the epidermal growth factor receptor pathway and deactivates various tumor-suppressing proteins, culminating in cellular proliferation and epithelial differentiation. These mechanisms result in “cauliflower-like” exophytic growth lesions, typical of RRP [2,7]. These lesions occur most often in transitional areas between the squamous epithelium and the ciliated columnar epithelium [2,7,11,17].

Papillomas appear as individual or multiple nodules. The nodules can appear as exophytic, sessile or pedunculated lesions, generally limited to the larynx, but quite often affecting the vocal cords, ventricular pleats, subglottis, and laryngeal surface of the epiglottis [2]. However, they may occur in any part of the aero-digestive tract and extend to the tracheobronchial tree and pulmonary parenchyma [2,3,18]. Involvement of the distal airway occurs in only 2–5% of patients with papilloma of the larynx, and the pulmonary parenchyma is affected in about 1% of cases [3,8,18–20].