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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].

Various hypotheses have been proposed to explain the distal spread of laryngeal papillomatosis, such as the extension of papillomas by contiguity, diffuse viral contamination, and iatrogenic factors, such as laryngoscopy, bronchoscopy, tracheostomy, and surgical manipulation [3,8]. High-risk factors for the spread of RRP toward the lower respiratory tract include HPV-11 infection, age <3 years, tracheostomy performed to avoid airway obstruction, and previous invasive procedures [7,16]. Compromise of the distal airway in the absence of papillomatosis lesions in the larynx is very uncommon [7].

Although it occurs rarely, RRP has the potential for malignant transformation, mainly to bronchogenic squamous cell carcinoma [2,3,9], which can occur decades after disease onset, generally in patients with prior spreading to the tracheobronchial tree [3]. Furthermore, malignant transformation rarely occurs in the laryngeal form of the disease, with no involvement of the distal airway [3]. The rates of malignant transformation are <1% in children and 3–7% in adults [2]. Risk factors include infection with high-risk HPVsubtypes (16 and 18), smoking, previous radiotherapy, cytotoxic drug use, p53 gene mutation, and high severity score or high activity of 2′-5'-oligoadenylate synthetase [7,10]. Although considered to be low risk, HPV subtypes 6 and 11, especially subtype 11, also display the potential for malignant degeneration [10,11]. The precise pathogenesis of malignant transformation remains uncertain. However, the oncogenic power of HPV has been attributed to interference in the cellular cycle, which alters the control of cellular differentiation [2,6,7,11].

5. Clinical manifestations

The clinical course of RRP is variable, with spontaneous remission occurring in a minority of cases. In the majority of cases it is aggressive, requiring multiple surgical treatments and adjuvant medical therapy [2,21]. RRP usually presents with nonspecific symptoms of airway involvement, including chronic cough, hoarseness, wheezing, voice change, stridor, and chronic dyspnea [2,3,7,21–23]. In children, the characteristic clinical profile of RRP is the triad of progressive hoarseness, stridor, and breathing difficulty. In adults, hoarseness is the most common finding [3]. Physical examination can reveal wheezing, stridor, tachypnea, and accessory muscle recruitment during respiration [3,7]. In severe cases, patients develop airway obstruction and respiratory distress [2,3,7]. Because of this nonspecific clinical scenario, the disease can mimic common laryngeal and respiratory pathologies, such as laryngitis, asthma, bronchitis, and croup; it is easily misdiagnosed, especially in children [2,21]. Consequently, many patients are treated for these complaints but do not respond; the disease worsens, evolving to severe respiratory insufficiency related to obstruction of the central airway [8]. This unpredictable course poses challenges for clinicians [2], often delaying diagnosis; average times from symptom onset to diagnosis range from 1 to 8 years [2,6]. Although basically benign, RRP causes significant morbidity and, in some cases, mortality due to recurrence and spread throughout the respiratory tract. Severe exacerbation necessitates frequent surgical procedures [2]. Peripheral dissemination may lead to recurrent pneumonia, obstructive atelectasis, and malignant degeneration, with symptoms that include fever, cough, hemoptysis, and progressive dyspnea [24]. Hemoptysis is common in these cases, and RRP is commonly confused with active tuberculosis [24]. In children, the symptoms tend to be more severe due to the rapid growth of lesions and propensity for airway obstruction [1]. Whereas some children require no more than semiannual surveillance, other need frequent admissions due to rapid lesion progression [21].

6. Diagnosis

RRP is rarely diagnosed based on chest X-ray findings [7]. In patients with lung involvement, chest X-rays may demonstrate solid or cavitated pulmonary nodules (Fig. 1). Rarely, vegetant, nodular sessile or pedunculated lesions are seen in the trachea and main bronchi [3].

Helical CT is the standard imaging modality for the assessment of RRP. It has shown a high degree of accuracy in the identification and characterization of tracheobronchial and pulmonary lesions [8]. CT findings of tracheal and bronchial lesions may suggest the diagnosis of RRP [3]. Tomographic findings include focal or diffuse airway narrowing caused by the nodular vegetant lesions, which occur on the mucosal surface, projecting into the lumen. In the trachea and main bronchi, localized or diffuse nodular narrowing may be found, as well as pedunculated or sessile nodular vegetant lesions. CT features of lung involvement in RRP consist of single or multiple multilobulated,well-defined, solid nodular or polypoid lesions of various sizes, with a centrilobular distribution, scattered throughout the lungs with a tendency toward confluence. The nodules may enlarge, frequently becoming air-filled cysts, and they may form large cavities with irregular internal borders and thick or thin walls [3,8,24] (Fig. 2). Lesions are more numerous in the basal and posterior regions of the lungs. Superimposed infection of cavitated lesions may show air-fluid levels [24]. Other CT findings related to airway obstruction and secondary infections are atelectasis, consolidations, air trapping, and bronchiectasis. Lymph node enlargement and pleural effusion are rarely seen, except in cases of malignant transformation [3]. Regular followup with CT is recommended due to the possibility of malignant transformation [8]. When malignant transformation occurs, CT may show enlargement of nodular lesions of the lung (Fig. 3), bronchi, or trachea, in association with numerous enlarged lymph nodes in the mediastinum and neck [25].

Virtual bronchoscopy is an alternative method for CT-based assessment of the tracheobronchial tree. It enables visualization of the airways on three-dimensional images, after processing using specific imaging protocols. This noninvasive method has the advantage of avoiding possible complications of conventional bronchoscopy, such as perforation, infection, and hemorrhage. Furthermore, the presence of airway stenosis is not a limiting factor, as this method enables visualization of the trachea and bronchia beyond the region of stenosis [9]. Magnetic resonance imaging can

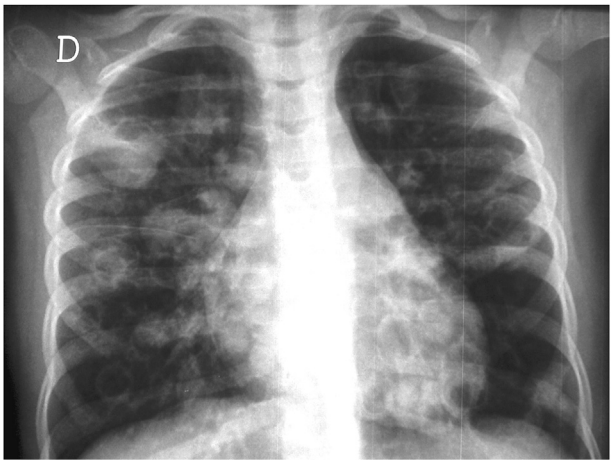

Fig. 1. A 6-year-old boy with RRP. Frontal chest X-ray shows multiple nodular cavitated lesions scattered throughout the lungs.

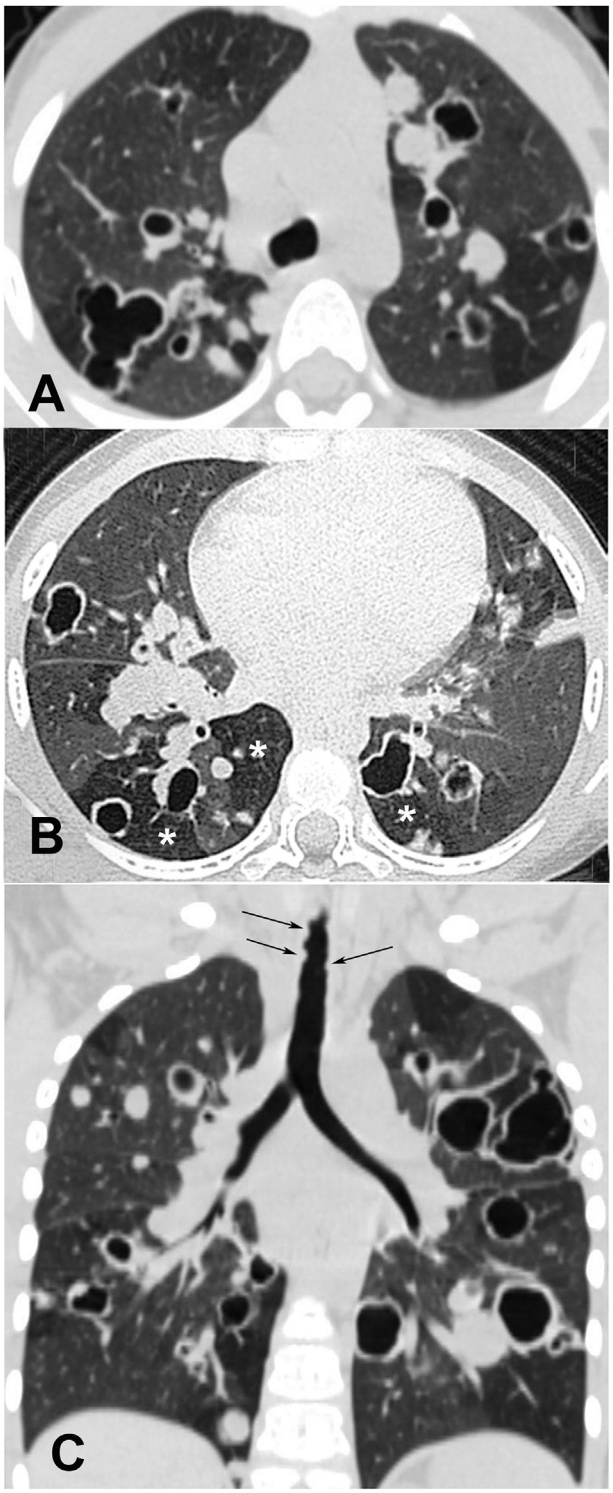

Fig. 2. A 6-year-old boy with RRP. Axial CT images with lung window settings at the levels of the upper (**a**) and middle (**b**) lung regions, and coronal reformatted image (**c**) show small polypoid lesions in the trachea (arrows in **c**), in association with multiple well-defined nodules scattered throughout the lungs, most of which are cavitating with thin and thick walls, as well as sparse air-trapping areas (white asterisks in **b**).

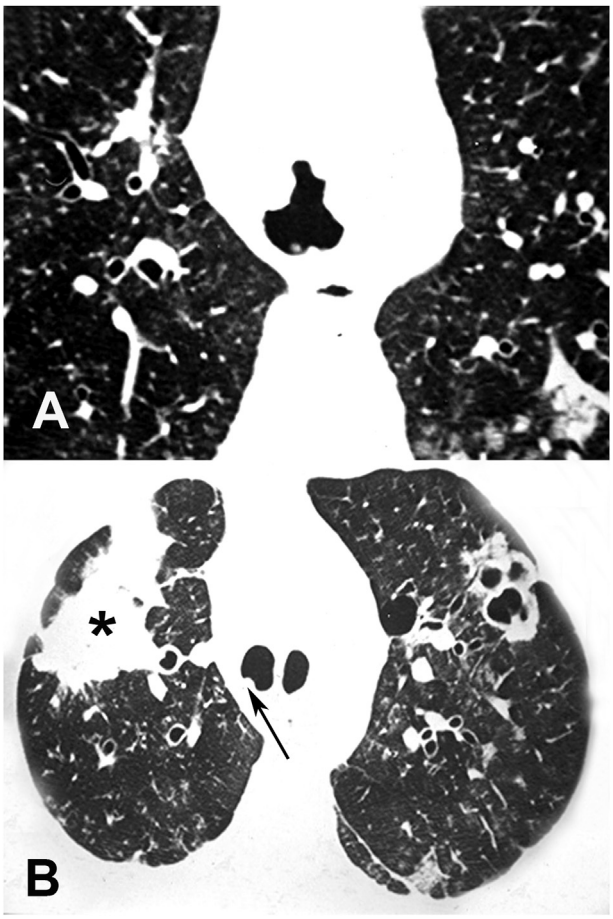

Fig. 3. An 18-year-old man with RRP. **a** Axial CT image obtained with lung window settings at the level of the carina shows airway narrowing caused by nodular vegetant lesions. **b** Axial CT image obtained with lung window settings at the level of the upper lung regions shows an ill-defined solid mass with irregular margins in the right upper lobe (asterisk), corresponding to squamous cell carcinoma. Note also cavitated confluent lesions in the left upper lobe, and a small papilloma in the right main bronchus (arrow).

show laryngeal, tracheobronchial, and pulmonary lesions, but its role in the diagnosis of RRP has not been well evaluated, with no prospective study conducted to date [26]. RRP lesions may show uptake on18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDGPET/CT) due to elevated cellular proliferation [25]. However, 18F-FDGPET/CT does not seem to be a useful tool for the early detection of malignancy in RRP [25,27]. Heterogeneous uptake of 18F-FDG among RRP lesions has been described, suggesting significant variability in the underlying metabolic behavior of the lesions [27].

Confirmatory diagnosis of RRP is made by direct laryngoscopy or fiberoptic bronchoscopy. Bronchoscopy is the most reliable method for the diagnosis of RRP lesions of the central airways, as it enables direct visualization of the lesions, assessment of the coloration of the tracheobronchial tree mucosa, and collection of biopsy samples for histopathological diagnosis and viral typing. Bronchoscopy is also useful for therapeutic planning. Papillomas appear as whitish polypoid lesions with clean and smooth surfaces, localized in the larynx, trachea, and/or bronchi [3,6,18]. Histopathological assessment of these lesions ensures the definitive diagnosis of RRP [3,21].

7. Pathology

Papillomas appear as exophytic masses or nodules, which are sessile or pedunculated, soft, and friable. Most papillomatous lesions arise at anatomical sites that contain juxtaposed epithelium,

including the limen vestibule, the nasopharyngeal surface of the soft palate, the midline of the laryngeal surface of the epiglottis, the upper and lower margins of the ventricle, the undersurface of the true vocal folds, the carina, and the bronchial spurs [3]. The mucosa appears velvety when papillomas remain microscopic, in contrast to the typical pinkish-whitish "cauliflower-like" presentation of the exophytic form [6].

Histologically, papillomas appear as projections or multiple fronds with central fibrovascular cores covered by stratified squamous epithelium [6]. Typical findings include hyperplasia of basal cells and large vacuolated epithelial cells with clear cytoplasm [3,6,8,13]. HPV also leads to a delay in epithelial maturation, resulting in basal layer thickening and an increased number of nucleated cells in the suprabasal layer of the stratified epithelium. Cellular differentiation has been noted to be abnormal, with altered keratin expression and production [13]. When the lesions extend to the tracheobronchial tree, the epithelium can be squamous or ciliated and cylindrical [3].

Pulmonary lesions have a different morphology, appearing as foci of squamous epithelium that grow circumferentially within the alveoli, supplied by the alveolar vascularization [3]. Areas of necrosis and degeneration are typically found in the central portion of a pulmonary lesion [3]. On the periphery, squamous cells invade the adjacent alveoli by extension. Lymphocytes and macrophages are also identifiable in the alveolar content. These lesions grow, coalesce, and destroy the pulmonary parenchyma, forming cavities [3,8]. Although papillomas are histologically benign, dysplasia and malignant changes may occur [3]. In cases of malignant transformation, pathological findings include sheets of polygonal tumor cells with abundant eosinophilic cytoplasm and vesicular nuclei, foci of keratinization, atypia, focal necrosis, and a variable mitotic rate, with microinvasive growth. Moreover, expression of cytokeratin 5 and 6, detected by immunohistochemical analysis, indicate epithelial origin [26].

8. Differential diagnosis

The differential diagnosis of RRP includes focal and diffuse central airway diseases [18]. Focal involvement occurs primarily with tracheal neoplasms, lesions of traumatic origin, post-intubation stenosis, some infectious diseases, and various systemic diseases that may involve the airways and lead to focal stenosis [18,24]. Diffuse involvement occurs in a wide array of conditions, including granulomatosis with polyangiitis (Wegener's granulomatosis), amyloidosis, tracheobronchopathia osteochondroplastica, relapsing polychondritis, tracheobronchomegaly, tuberculosis and other granulomatous infections, neurofibromatosis, and sarcoidosis [18,24]. Bronchoscopy remains the primary procedure for the diagnostic workup of these disease entities. Nevertheless, in cases of clinical or radiological suspicion of tracheobronchial alteration, further evaluation using CT is of great importance [3]. The aspect and location of lesions, the presence and location of calcifications, and association with abnormalities of the pulmonary parenchyma, as well as correlation with the clinical data, can suggest a specific diagnosis and aid in the planning of bronchoscopy or therapeutic intervention [8,24]. Hence, the clinical features of central airway involvement, in association with the bronchoscopic or tomographic finding of tracheal or bronchial wall thickening with irregular luminal narrowing, as well as nodular or polypoid noncalcified lesions, are highly suggestive of RRP. The additional finding of distal spread with parenchymal nodules, usually cavitated, makes the diagnosis of RRP even more likely. Ultimately, histopathological findings establish the diagnosis [1,18,24].

9. Treatment

Although no definite curative treatment for RRP exists, surgical excision of the papillomas remains the mainstay of treatment, to ensure the functioning of the airway and maintain the quality of phonation [1,2,11,28]. The goal of surgery is to debulk the papilloma as much as possible without damaging normal structures [22]. HPV is present in mucosa that appears outwardly to be macroscopically unaffected, and distinguishing infected cells with normal appearance from uninfected epithelia is currently not possible [11].

Surgical complications, such as respiratory tract burns, severe laryngeal scarring and stenosis, and tracheoesophageal fistulae, have prompted rapid conversion from the use of lasers to the adoption of microlaryngeal surgery with microdebriders [1,27]. The ability to perform precise debridement with a microdebrider, with limited damage to the underlying tissues and greater preservation of normal epithelium, is useful in the treatment of RRP, which often necessitates multiple interventions [1]. Despite the adoption of new techniques and progressively modern surgical equipment, serious surgical complications, such as synechia of the larynx and glottic stenosis, still occur, particularly in patients who undergo multiple procedures [1]. Lesion recurrence after surgical procedures is common. The persistence of the viral genome in the remaining tissue is believed to be the principal explanation for such recurrence [2].

Tracheostomy may be required for more extensive disease with a serious risk of laryngeal airway obstruction, especially when multiple interventions have failed [1,10,11]. Compared with HPV subtype 6, infection with HPV 11 appears to be more likely to result in tracheostomy [10]. When tracheostomy is inevitable, decannulation must be performed as soon as the airway is considered to be stable and the disease is controlled, as it provides an additional site for rapid viral colonization and serves as a conduit for the distal spread of the disease [1]. Unfortunately, about half of patients who undergo tracheostomy develop tracheal papillomas [6].

About 20% of patients with RRP require adjunctive medical treatment in addition to surgery to control the disease [2]. The current criteria for adjuvant therapy are the requirement for more than four surgical procedures annually, rapid recurrence of papillomas with airway compromise, and distal multisite spread of the disease [2]. The majority of treatments by medication act in immunomodulation and the inhibition of HPV replication and proliferation. Medications used in such treatment include interferon, antiviral agents (acyclovir, ribavirin, cidofovir), retinoids, and inhibitors of the oxigenase-2 cycle [2].

One of the first adjuvant treatments for RRP was interferon, which produced positive results in terms of disease evolution in some patients [2], leading to the reduction of lesion growth [16]. The main limitation related to the intravenous administration of interferon is systemic toxicity, with a reversible increase in the serum transaminase level, and possible leucopenia and thrombocytopenia [1]. Common side effects include transient fever, fatigue, nausea, arthralgia, and headache, along with spastic diplegia in infants [1]. Recently, the topical delivery of interferon alpha via the biphasic vesicles has been investigated, but further studies in patients with RRP are needed [1]. Cidofovir, an analog of cytosine, is currently the most commonly used antiviral in medical adjuvant treatment for RRP [1,21]. It can be administrated intravenously, via nebulization, or by intralesional injection. In prospective studies, adjuvant intralesional cidofovir administration has led to the partial to total regression of lesions and reduction of the frequency of surgical procedures [1,21]. Intralesional administration has the advantage of maintaining plasma levels below those leading to toxicity, with no local side effect [1,12,21]. The long-term risks associated with the intralesional administration of cidofovir are not

well known, but include the theoretical risk of malignant transformation [21].

The advent of vaccines against HPV offers potential for the future eradication of the disease, by reducing the incidence and, consequently, transmission of the virus. The quadrivalent vaccine is indicated for the prevention of cervical and anogenital cancers and pre-carcinogenetic lesions associated with subtypes 6, 11, 16, and 18 [22]. The vaccine also holds promise for patients already affected by RRP. However, current isolated positive experiences need to be validated by multicenter trials, which may determine the true benefits of vaccination as a treatment for RRP [1]. Currently, HPV vaccines are not approved for routine use in neonates; this application requires further research [6].

10. Conclusion

RRP is basically a benign disease, characterized by the appearance of papillomatous lesions anywhere in the aero-digestive tract. Children and young adults are affected most commonly. The disease is typically restricted to the larynx, but it can become aggressive, resulting in persistent or recurrent involvement of the nasopharynx and tracheobronchial tree. Distal spreading to the pulmonary parenchyma occurs in about 1% of cases. The natural history of RRP is quite variable, including spontaneous regression, persistence, and dissemination of lesions causing airway compromise and, in rare instances, progression to squamous cell carcinoma. RRP may cause significant morbidity and, in some cases, mortality due to recurrence and spread throughout the respiratory tract; severe exacerbation necessitates frequent surgical procedures. Knowledge of the etiology, clinical manifestations, and characteristic bronchoscopic and imaging aspects of the disease is essential to suggest a correct diagnosis, which must be confirmed by histopathology. Unfortunately, no definitive curative treatment for RRP is currently available, and surgery remains the mainstay of treatment.

Conflict of interest statement

All authors inform that there are none conflicts of interest.

Contributions of each author

Dr. Forte: contributed to data interpretation, statistics, and preparation and revision of the manuscript.

Dr von Ranke: contributed to the collection of the data and preparation of the manuscript.

Dr Escuissato: contributed to CT scan evaluation and final review of the manuscript.

Dr Araujo Neto: contributed to the data interpretation, literature review, and revision of the manuscript.

Dr Zanetti: contributed to CT scan evaluation, literature review, and revision of the manuscript.

Dr Hochhegger: contributed to the design of study, CT scan evaluation, and final review of the manuscript.

Dr. Souza: contributed to CT scan evaluation, statistics, and final review of the manuscript.

Dr Marchiori was the principal investigator and is the guarantor of the entire manuscript. He contributed to the coordination and design of the study, data interpretation, and preparation and revision of the manuscript.

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