Recurrent respiratory papillomatosis (RRP) is a rare, difficult to treat benign tumor disease of the respiratory tract with a progressive course caused by human papillomavirus and most often occurs in the larynx in the form of papillomas. They may be present at any age, but most often between the ages of 1 and 4. They can recur after treatment, undergo malignant transformation, and spread to the vocal cords, trachea, or lungs.

Objective — to present our own observation of the malignant transformation of RRP in a young man of 23 years old, who was diagnosed and treated at the SO «National Institute of Phthisiology and Pulmonology named after F.G. Yanovsky of the NAMS of Ukraine».

Materials and methods. Prior to this non-systematic review, information was searched in MEDLINE/PubMed for systematic reviews, meta-analyses, and randomized controlled trials published in the past 5 years using such terms as human papillomavirus, recurrent respiratory papillomatosis, and malignant transformation.

Results and discussion. Patient H, 23 years old. From the anamnesis, it is known that the diagnosis of RRP was made at the age of 4, since then he regularly noticed the appearance of dry wheezing, shortness of breath, hoarseness, and sometimes its disappearance. Since childhood, the patient has been under the supervision of a pediatric otolaryngologist. The papillomas were localized on the vocal cords. It is known that more than 100 procedures were performed to remove papillomas using electrocoagulation under general anesthesia. For morphological verification of the diagnosis, it was decided to perform a video-assisted thoracoscopic surgery of the right lung.

Pathological examination findings: «Respiratory papillomatosis with a tendency to malignant transformation». The biopsy material was sent for the immunohistochemical examination. Findings: «G2 Non-keratinizing squamous cell lung carcinoma. There are signs of lymphovascular, perineural invasion, there are signs of pleural invasion, the immunohistochemical study shows that tumor cells are positive for p40, which allows to confirm the diagnosis». After that, the patient was consulted by an oncologist and an immunologist. A 2-component chemotherapy with Carboplatin and Paclitaxel was prescribed.

Conclusions. RRP is a rare disease that can become malignant in case of untimely diagnosis and inadequate screening. Great attention should be paid to complementing of the surgical treatment with vaccination and immunotherapy.

Keywords
Recurrent respiratory papillomatosis, malignisation, human papillomavirus.

Recurrence of respiratory papillomatosis (RRP) is a rare, difficult to treat benign tumor disease of the respiratory tract with a progressive course caused by human papillomavirus (HPV). RRP was first described in the 1800’s, but connection between HPV and RRP was made only in the early 1980’s. RRP can occur in both childhood and adulthood. Multiple studies have shown that the most likely route of transmission of HPV in RRP is from mother to child during labor. Adult patients may be exposed during sexual contact [2]. RRP most often occurs in the larynx in the form of papillomas. They may be present at any age, but most often between the ages of 1 and 4. They can
recur after treatment, undergo malignant transformation, and spread to the vocal cords, trachea, or lungs [4]. The disease can manifest itself as a weak cry in children, hoarseness, cough, shortness of breath, dysphagia, and, in severe cases, it may cause airway obstruction.

In the diagnosis of RRP, the helical computed tomography (HCT) reveals distinctive nodular, infiltrative-destructive shadows of various sizes scattered throughout the lungs. The 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. The definitive diagnosis of RRP is based on the histopathological analysis. Also, depending on the localization, laryngoscopy can be used.

The lesion can be either single or multiple. RRP is the most common benign neoplasm of the larynx among children, characterized by a high frequency of multilocal recurrence, and is accompanied by a decrease in the patient’s quality of life. The spread to the lung is rare and accounts for less than 1 % of all lung tumors [3].

The treatment of RRP is surgical. Since the growths can recur after weeks or months, several removal procedures may be required. Follow-up with laryngoscopy and bronchoscopy is also necessary. Pulsed laser therapy, electrocoagulation, or photodynamic therapy can be used for excision [5]. In severe cases, antiviral (e.g., Cidofovir) or antitumor (e.g., Bevacizumab) drugs are used. In some patients, the lesions may regress during puberty. According to the literature, if there is a recurrence after four surgical procedures within 12 months, the additional therapy should be prescribed [11]. In cases where airway patency is severely impaired, the tracheotomy may be prescribed [6]. HPV vaccination plays a key role in the prevention of RRP [8]. Studies have shown a decrease in incidence and prevalence after vaccination, indicating its potential therapeutic use [9]. Quadrivalent and 9-valent HPV vaccines are used. The immunotherapy also has a potential role in the treatment of RRP due to the pathophysiology of RRP and new evidence that HPV infection causes immune dysregulation, which is a promising area of research [10].

Objective — to present our own observation of the malignant transformation of RRP in a young man of 23 years old, who was diagnosed and treated at the SO «National Institute of Phthisiology and Pulmonology named after F.G. Yanovsky of the NAMS of Ukraine».

Materials and methods
Prior to this non-systematic review, information was searched in MEDLINE/PubMed for systematic reviews, meta-analyses, and randomized controlled trials published in the past 5 years using such terms as human papillomavirus, recurrent respiratory papillomatosis, and malignant transformation.

Results and discussion
Clinical case study. Patient H., 23 years old, presented with a medical history indicating that the diagnosis of RRP was made at the age of 4. Since then, he has regularly experienced symptoms such as dry wheezing, shortness of breath, hoarseness, and occasional disappearance of symptoms. Since childhood, the patient has been under the supervision of a pediatric otolaryngologist. The papillomas were localized on the vocal cords. According to the patient’s mother, it is known that more than 100 procedures were performed to remove papillomas using electrocoagulation under general anesthesia. The interval between recurrences and the need for the repeated removal of the vocal cord lesions was variable. The shortest time between the coagulations was 1 month. The patient has not received HPV vaccination and immunotherapy. 5 years ago, he visited a doctor with complaints of fever up to 38, wet cough, weakness, and sweating. Chest X-ray and helical CT scan were performed (Fig. 1).

The clinical and radiological findings were interpreted as bronchiectasis, bullous emphysema, and bilateral multisegmental pneumonia. The antibiotic therapy was prescribed. The patient’s condition improved against the background of the conservative treatment. After 4 years, the complaints recurred, and progression of the process was noted during helical CT scanning, which led to the diagnosis of cystic pulmonary hypoplasia. The following year,
the patient had signs of acute respiratory viral infection, suspected coronavirus infection, and chest X-ray and helical CT of the thorax, which revealed the occurrence of new and enlargement of existing areas of destruction: «In the parenchyma of both lungs, growing in the caudal direction, the hollow formations ranging in size from 8 mm to 89 × 62 mm were found. Disseminated process in the lungs (pulmonary aspergillosis?), progression of the process» (Fig. 2 and 3).

To exclude the autoimmune systemic disorder of the connective tissue, systemic vasculitis, tests were performed to determine antinuclear antibodies, proteinase-3, myeloperoxidase. The result was negative. For morphological verification of the diagnosis, it was decided to perform a video-assisted thoracoscopic surgery of the right lung.

Surgery description: After treating the skin with antiseptic, under anesthesia with one-lung ventilation, the right pleural cavity was reached with the help of 3 thoracoports. On examination, there is no pleural effusion in the cavity, there are isolated adhesions, areas with dense foci on the lung, the parietal pleura is unchanged. With the help of an endostapler, a biopsy of a lobe of the right lung with a lesion was performed. The hemostasis was performed, 2 drains into the pleural cavity.

Pathological examination findings: Respiratory papillomatosis with a tendency to malignant transformation. The biopsy material was sent for the immunohistochemical examination. Findings: G2 Non-keratinizing squamous cell lung carcinoma. There are signs of lymphovascular, perineural invasion, there are signs of pleural invasion, the immunohistochemical study shows that tumor cells are positive for p40, which allows to confirm the diagnosis. After that, the patient was consulted by an oncologist and an immunologist. A 2-component chemotherapy with Carboplatin and Paclitaxel was prescribed.

Since RRP has a predominantly benign course and malignant transformation is quite rare, there are not many publications on the malignant transformation. In our observation, there was a young man with a long-proven history of RRP since early childhood. However, a case of RRP malignant transformation in a 53-year-old man was described [12]. In 2018, he was diagnosed with obstructing respiratory papillomatosis of the trachea and underwent repeated bronchoscopic debulking procedures. These were complicated by tracheoesophageal fistula, which required several surgical interventions. Thereafter, the papillomas of the trachea recurred, and the
patient had repeated bronchoscopic removals. A computed tomography showed bilateral small lung nodules that progressed to cavitary nodules. The biopsy of the cavitary nodules showed focal atypical squamous proliferation. Given the progression of the cavitary nodules, a repeat biopsy was performed and squamous cell carcinoma was reported. In addition to surgery, the patient started therapy with Carboplatin and Pembrolizumab. Overall, the patient had a total of 14 therapeutic bronchoscopies before developing a pulmonary disease that progressed to squamous cell carcinoma. Unfortunately, the patient’s cancer progressed further, and he was transferred to hospice [12].

Yang and colleagues studied the course of RRP in juveniles. Compared with the patients without lung involvement, the patients with lung involvement had a younger age of onset, a higher incidence of surgical interventions, a higher mortality rate (OR = 94.909), and an increased risk of tracheotomy that could not be decannulated (p < 0.001) [13].

Papaioannou analyzed the course of the disease and showed that the treatment of choice is the surgical excision with the CO₂ laser combined with the quadrivalent or polyvalent vaccine. Consequent vaccination of both boys and girls has the potential to reduce the occurrence of RRP [7].

**Conclusions**

RRP is a rare disease that can become malignant in case of untimely diagnosis and inadequate screening. Great attention should be paid to complementing the surgical treatment with vaccination and immunotherapy.

There is no conflict of interest.

**Participation of the authors:** research concept and design — M.S. Opanasenko, O.V. Tereshkovych, S.M. Shalahay; collection of material — S.M. Shalahay; material processing — S.M. Shalahay, O.D. Shestakova, L.I. Levanda, M.I. Kalenychenko, V.I. Lysenko; editing of the text — O.D. Shestakova, M.Yu. Shamray, S.M. Shalahay.

**References**

Випадок малігнізації рецидивного респіраторного папіломатозу

Рецидивуючий респіраторний папіломатоз (РРП) — рідкісне добрякісне пухлинне захворювання дихальних шляхів з прогресуючим перебігом, яке важко піддається лікуванню, викликається вірусом папіломи людини і найчастіше виникає в горлі в уяві утворення папілом. Вони можуть трансформуватись у будь-якому віці, але найчастіше від 1 до 4 років. Вони можуть рецидивувати після лікування, піддаючись злоякісній трансформації та поширюватися на голосові зв'язки, трахею або легені.

Мета роботи — представити власне спостереження малігнізації РРП у молодого чоловіка 23 років, що проходив діагностику та лікування у ДУ «Національний інститут фтизіатрії і пульмонології імені Ф.Г. Яновського НАМН України».

Матеріали та методи. Інформацію шукали в MEDLINE/PubMed для систематичних оглядів, метааналізу та рандомізованих контрольованих досліджень, опублікованих за останні 5 років, використовуючи терміни: вірус папіломи людини, рецидивний респіраторний папіломатоз, малігнізація.

Результати та обговорення. Хворий Х. 23 роки. За анамнезу відомо, що діагноз РРП був поставлений у віці 4 років, з того часу регулярно відмічав появу сухих хрипів, задишки, захрипlostі, іноді її зникнення. З дитинства хворий перебуває під наглядом дитячого отоларинголога. Папіломи локалізувалися на голосових зв'язках. Відомо, що було проведено більше 100 процедур з видалення папілом за допомогою електрокоагуляції під загальним наркозом. Для морфологічної верифікації діагнозу було вирішено провести відеоторакоскопічну (VATS) біопсію правої легені.

Дани патологоанатомічного дослідження: «Респіраторний папіломатоз зі схильністю до злоякісної трансформації». Біоптат направлений на імуногістохімічне дослідження. Результати: «G2 Плоскоклітинна карцинома легень, яка не ороговіває». Є ознаки лімфосудинної та периневральної інвазії, імуногістохімічне дослідження показує, що в таких клітин позитивні на p40, що дає змогу підтвердити діагноз. Після цього хворий був консультований онкологом та імунологом. Призначена 2-компонентна хіміотерапія карбоплатином і паклітаном.

Висновки. РРП — рідкісне захворювання, яке може малігнізуватись при несвоєчасній діагностиці та неадекватному обстеженні.

Ключові слова: рецидивний респіраторний папіломатоз, малігнізація, вірус папіломи людини.