next two days the patient complained of increasing, nonproductive cough, chest tightness, headache and dizziness. Auscultation of the chest revealed scattered rhonchi and rales at the left base. An erythematous, maculopapular, nonpruritic eruption was present on the upper arms, thighs and chest. Sputum smear revealed marked eosinophilia and peripheral blood smear showed 30 percent eosinophils, with a total leukocyte count of 9,000. Mysoline was substituted for carbamazepine therapy. Over the next nine days there was resolution of pulmonary symptoms, clearance of skin rash and a decrease in both sputum and blood eosinophilia. As an outpatient, there has been no recurrence of symptoms.

**DISCUSSION**

Although diphenylhydantoin (Dilantin) has been associated in the past with hilar adenopathy, a drug-induced systemic lupus erythematosis-like syndrome, miliary pulmonary infiltrates and abnormalities in oxygen transfer, to our knowledge, carbamazepine has only recently been incriminated as causing pulmonary disease. Careful review of our patient’s history served to exclude exposure to toxic inhalants or use of other drugs. The increases in serologic titer for *M. pneumoniae* suggest that the pulmonary syndrome was secondary to infection with this agent. Modest eosinophilia, carbon dioxide retention, and a diffuse interstitial infiltrate have all been reported in *M. pneumonia*. Nevertheless, the reappearance of this syndrome on re-exposure to the drug serves to implicate carbamazepine as the etiologic agent. In the previously reported case of pulmonary hypersensitivity to carbamazepine, the patient had concomitant pulmonary tuberculosis. It is possible that the presence of infection might enhance the development of drug reactions. Carbamazepine should be added to the list of agents which can produce hypersensitivity pneumonitis.

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**Papillomas of the Tracheobronchial Tree with Malignant Degeneration***

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Papillomas are rare tumors of the respiratory tract, which are usually considered benign. We studied a male patient with adult onset of squamous papillomatosis involving both the trachea and the bronchi, with malignant degeneration. When we obtained specimens bronchoscopically, only the bronchial lesions showed carcinomatous changes. Thoracotomy demonstrated carcinoma in the tracheal lesion as well. We conclude that transbronchoscopic biopsy may be inadequate in the evaluation of papillomatosis.

Squamous papilloma is a common laryngeal tumor in children, and in 1-2 percent of cases, lesions, usually multiple, occur also in the lower respiratory tract. In adults with the tumor, lesions are present in the tracheobronchial tree but more frequently without prior laryngeal involvement. Papillomas are generally considered benign. However, adult-onset cases and those juvenile-onset cases which have been irradiated, have been associated with malignant degeneration to squamous cell carcinoma. Often, tracheobronchial papillomas can be visualized through the bronchoscope and biopsy specimens may be obtained. Such superficial biopsy procedures may be misleading. Excision of the entire specimen by thoracotomy may be required to exclude the possibility of malignancy. In this case report, we emphasize the difficulty involved in the diagnosis of malignant degeneration in adult-onset squamous papillomas.

**CASE REPORT**

A 57-year-old white male was admitted to the Cleveland Veterans Administration Hospital complaining of productive cough, left-sided pleuritic chest pain and exertional dyspnea of one-month duration. He had no fever or chills. Over the preceding six months he had lost 9 kg without a decrease in appetite. Physical examination revealed a temperature of 37.7°C (99.9°F); other vital signs were normal. There was dullness at the right base of the lung, with decreased breath sounds and tactile fremitus in this area. Mild expiratory wheezes were heard on the right. There was no lymphadenopathy. The rest of the physical examination was normal.

The leukocyte count was 12,000/mm³, with a shift to the left. Other laboratory data were normal. Sputum Gram-stain revealed a mixture of organisms. Sputum culture grew normal flora. The intermediate-strength purified protein derivative (PPD) was nonreactive. Sputum smears for acid-fast bacilli were negative. Chest x-ray film revealed a right lower lobe infiltrate and complete collapse of the right middle lobe.

The patient was treated with penicillin, with symptomatic

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FIGURE 1. Gross surgical specimen of resected right middle and lower lobes showing appearance of papillomas in bronchus intermedius.

improvement but without chest x-ray film change. Fiberoptic bronchoscopy revealed a normal larynx. Extending between the third through fifth tracheal rings along the right lateral wall of the trachea, a pale, cauliflower-like, sessile mass protruded into the lumen. It was not of sufficient size to decrease the lumen appreciably. A second lesion appeared in the bronchus intermedius, completely occluding the right middle lobe orifice and partially occluding the orifice to the basal segments. A smaller satellite lesion was seen in the bronchus intermedius, distal to the first. The rest of the examination was normal. Multiple biopsies of each lesion revealed only normal squamous epithelium.

Further evaluation included rigid bronchoscopy with repeated, more extensive biopsies. During this procedure, there was considerable local hemorrhage. Histologic examination was compatible with a diagnosis of squamous papilloma. Mucosal invasion consistent with squamous cell carcinoma was seen on a single section from the biopsy of the proximal bronchial lesion. The tracheal specimens were considered benign.

The patient then underwent right thoracotomy, with removal of the right middle and lower lobes without complication. The resected specimen is shown in Figure 1. In a separate procedure, tracheal rings three through seven were resected via a cervical and median sternotomy.

Pathologic examination revealed a predominantly exophytic growth of squamous papilloma from the resected tracheal rings as well as from the bronchus intermedius. Although the cytologic features were benign, focal squamous carcinomatous changes were manifested in both lesions by the presence of an overt mural invasion through the cartilage plate and submucosal glands (Fig 2).

DISCUSSION

The exact etiology of respiratory tract papillomas is unknown. Various theories have been proposed, including localized areas of dysplasia with a possible genetic basis, localized trauma (as in tracheostomies in the juvenile group), cigarette smoking, and viral infection.

Patients with adult-onset papillomatosis are usually male and commonly present with wheezing, cough, dyspnea, hemoptysis and segmental pneumonia distal to an obstruction. All of these symptoms, with the exception of hemoptysis, were present in our patient.

The behavior of juvenile and adult-onset multiple papillomatosis appears to be different. Juvenile papillomatosis, almost uniformly, does not show malignant alteration unless there is a history of prior irradiation therapy. The propensity for malignant degeneration appears to be much greater in adults. Al-Saleem reported six cases of adult-onset papillomatosis, three of which indicated malignant change, and cited four other cases, two of which showed malignancy. The same risk of malignancy may exist in adults with solitary papilloma of the bronchus. Malignancy usually occurs in the form of a well differentiated squamous cell carcinoma, which extends by local invasion; however, one case of regional extrapulmonary node metastasis has been reported.

Bronchoscopic diagnosis and removal has been advocated for both juvenile and adult-onset squamous papillomas. In our patient, malignancy was demonstrated in only a single section of the bronchial papilloma obtained by bronchoscopy. It was demonstrated in the tracheal lesion only after excision by thoracotomy. Because the risk of malignancy is significant, and because bronchoscopic biopsies may be misleading, removal by thoracotomy should be considered in the treatment of all patients with adult-onset and in those patients with juvenile-onset of papillomatosis previously irradiated. Without the entire surgical specimen, the true character of this lesion may remain unrecognized.

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Figure 2. Section from bronchus intermedius. Squamous papilloma can be seen invading cartilage plate in right and submucosal glands in left lower portion of section (Hematoxylin and eosin stain, original magnification × 70).