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All that wheezes is not asthma

哮喘不等於患上哮喘

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Asthma is a common disease. Wheezing is not pathognomonic of asthma, however. One must be alert when appropriate asthmatic treatment does not provide adequate control. Other causes of airway obstruction must be considered, especially when stridor is heard. This report describes an elderly patient who had been managed as having asthma but had an endotracheal tumour.

哮喘是一種常見的疾病。然而，哮喘不是哮喘獨有的病徵。如果病人有喘鳴而哮喘療法未能有效地控制病況，醫生必須提高警惕，考慮其他氣管堵塞的原因。本報告描述一位年老患者，他的氣管內有腫瘤，卻被誤作哮喘治療。

Introduction

Wheezes, rhonchi, and stridor are musical adventitious sounds. The terminology is often confusing, and so are the physical signs. Wheezes are high-pitched, with dominant frequency of 400 Hz or more, and are whistling in quality. Rhonchi are continuous sounds longer than 250 milliseconds, and of a low-pitched, dominant frequency of approximately 200 Hz or less and snoring in quality. Stridor is predominantly inspiratory, best heard over the neck.¹ Stridor can be pitched high or low depending on the degree of obstruction. High-pitched stridor can be mistaken for wheezes, for which the following case history is an illustration.

A 65-year-old housewife was referred to the Respiratory Clinic for management of poorly controlled asthma. She was a non-smoker who had had six children. She had diabetes mellitus and was treated with tolbutamide and diet control. There was no family history of asthma or allergy and she had no history of childhood asthma. She had no occupational exposure to allergens, although her husband kept pigeons on the roof. She had developed progressive exertional shortness of breath (SOB) since her early 60s. These attacks had no relationship to the weather or seasons and there was no diurnal variability. Despite the SOB, she could still manage her daily household work. In early 1999 and again in May 2000, she was admitted to hospital for acute attacks of SOB. Wheezing was noted during physical examination and she was diagnosed as having asthma. Inhalational bronchodilators and steroids were prescribed, but her symptoms only improved slightly, with the medications only relieving her symptoms for 2 hours. Despite removal of the pigeons from her home, the SOB and wheezing persisted. Her condition progressively worsened and exercise tolerance decreased to only one flight of stairs. She later developed sporadic bloodstained sputum with severe cough. She moved to a new flat in 2001 and was admitted to hospital for 10 days for investigation of haemoptysis after a bout of coughing. Chest X-ray showed no abnormality. In August 2001, she was again admitted for SOB. Both oral and inhalational steroids, together with bronchodilators, were prescribed but the symptoms were not alleviated. She was then referred to the Respiratory Clinic for assessment.

Physical examination

There was an audible 'wheeze' heard at the patient's bedside. This was high pitched but inspiratory in timing. Her respiratory rate was 18 breaths per minute. There were no signs of clubbing or lymphadenopathy. On auscultation, no wheeze

Key words:

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 Lung neoplasms;
 Nasopharyngeal neoplasms

關鍵詞：

哮喘；
 癌；
 肺腫瘤；
 鼻咽瘤

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was audible. Air entry was decreased bilaterally. The ‘wheeze’ was in fact stridor. Her other systems were normal.

Investigation

The patient’s blood count showed that the white blood cell count was within the normal range at $5.3 \times 10^9/L$, as was her platelet count $278 \times 10^9/L$, although her haemoglobin level was low at 116 g/L (normal range, 120-150 g/L). Renal and liver function was normal. Chest X-ray was normal. Lung function test showed that pre-bronchodilator forced expiratory volume in 1 second (FEV_1) was 0.64 L (30% predicted) and pre-bronchodilator forced vital capacity (FVC) was 2.62 L (108% predicted). Forced expiratory volume in 1 second was reduced to 0.29 L (14% predicted), and FVC reduced to 2.22 L (85% predicted) after bronchodilator inhalation—a reduction of 55% and 22%, respectively. Pre-bronchodilator FEV_1/FVC was 23%. Forced expiratory flow (FEF) 25-75% was 0.42 L/sec (18% predicted). The peak flow rate was 33% predicted both before and after bronchodilator inhalation. Vital capacity was 96% predicted. Total lung capacity was 98% predicted. Residual volume was 106% predicted. Diffusing capacity of the lung for carbon monoxide was 118% predicted. Airway resistance was markedly increased to 1503% predicted. Spirogram showed an obstructive pattern. Flow-volume loop showed advanced intrathoracic inspiratory and expiratory obstruction (Fig 1). The presence of stridor suggested upper airway obstruction, and the presence of recurrent haemoptysis suggested the presence of an upper airway tumour. Bronchoscopy was performed and a multi-lobulated tumour was seen in the trachea just above the carina and almost completely obstructing the lumen (Fig 2).

The patient underwent emergency endobronchial removal of the tumour by rigid bronchoscopy. Histology of the tumour tissue showed syncytial sheets of carcinoma cells with oval vesicular nuclei and prominent nucleoli set in a background of dense lymphoplasmacytic infiltration (Fig 3). The diagnosis was tracheal lymphoepithelioma-like carcinoma (LELC). Blood serum taken after endoscopic removal of the tumour was negative for Epstein-Barr virus (EBV) immunoglobulin A (IgA) virus capsid antigen (VCA).

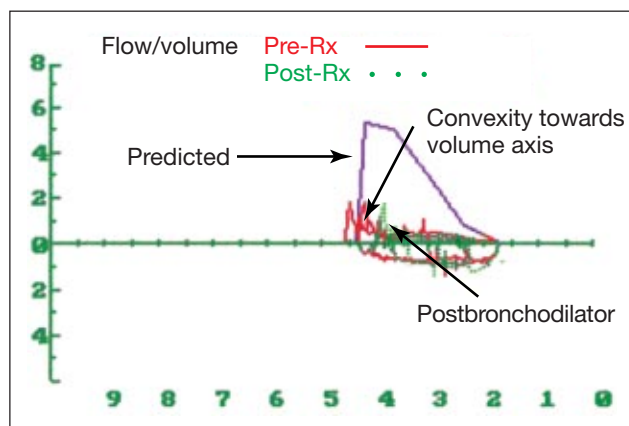


Fig 1. Flow-volume loop at diagnosis

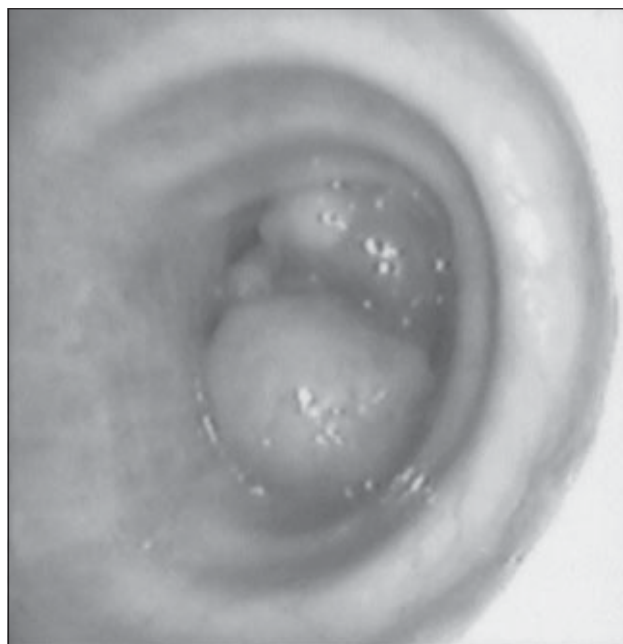


Fig 2. Bronchoscopy showed a multi-lobulated tumour at lower end of the trachea

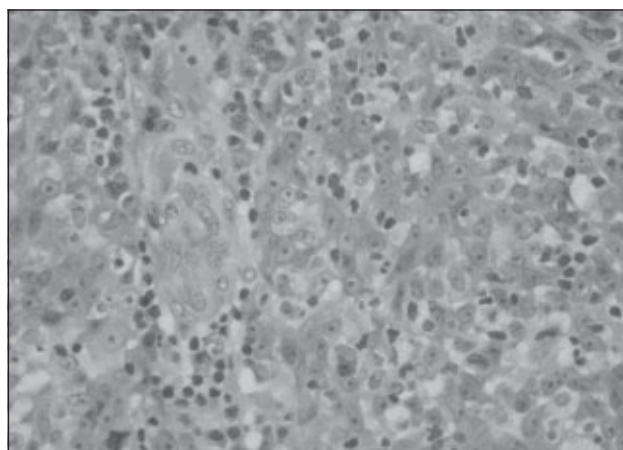


Fig 3. High-power H&E stain showed a syncytial network of tumour cells on a background of lymphocytes. Tumour cells showed large vesicular nuclei with prominent nucleoli

In situ hybridisation (ISH) of tumour tissue for EBV encoded RNA (EBER) was positive.

Nasopharyngeal examination showed no abnormality, and blind biopsy of the posterior nasopharynx did not show any nasopharyngeal carcinoma. The patient had 80% of her SOB relieved and the stridor disappeared. No wheezes or stridor could be heard at auscultation. Lung function tests after removal of the tumour showed that FEV_1 was 1.46 L (69% predicted), FVC was 2.92 L (112% predicted), FEV_1/FVC was 49%, and FEF25-75% was 1.22 L/sec (53% predicted). Post-surgery flow-volume loop showed marked improvement in both inspiratory and expiratory flow (Fig 4). Computed tomography of the thorax after removal of the tumour showed remnants of tumour tissue in the lower end of the trachea and a 1-cm lymph node was detected anterior to the trachea. Staging of the tumour was T_4N_2 , stage IIIB. Due to the position of the

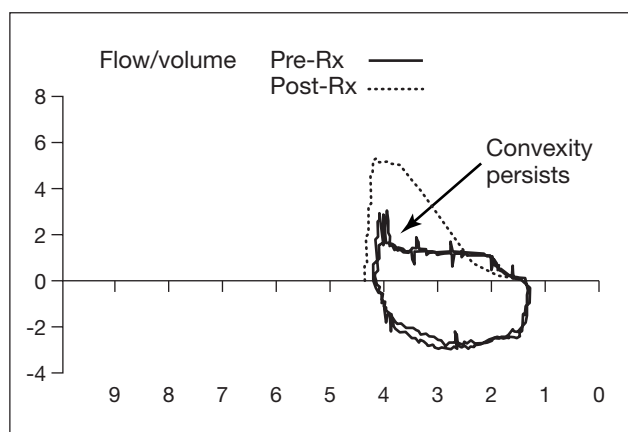


Fig 4. Flow-volume loop 1 month after coring of tracheal tumour

tumour, chemotherapy and radiotherapy were prescribed. There was complete clinical and radiological response. Follow-up positron emission tomography showed complete regression of the tumour and the mediastinal lymph node. The patient has survived to date in good health without SOB. Lung function tests at 11 months after diagnosis and 7 months after chemotherapy were as follows: FVC pre-bronchodilator 117% predicted and post-bronchodilator 127% predicted; FEV₁ pre-bronchodilator 119% predicted and post-bronchodilator 121% predicted; FEV₁/FEC pre-bronchodilator 82%, and post-bronchodilator 77%; FEF₂₅₋₇₅ pre-bronchodilator 118% and post-bronchodilator 131% predicted. Flow-volume at 11 months after diagnosis is shown in Fig 5.

Discussion

The prevalence of asthma among elderly Chinese people in Hong Kong is between 3.9% and 5.0%, depending on the definition.² Among elderly people with asthma, 65.5% developed asthma symptoms before the age of 50 years.³ Onset of asthma, however, can occur at any age. Among elderly people, atopy is less common and IgE is significantly lower than among younger people with asthma. The symptoms of asthma are severe in 42.1% of elderly patients and 93.0% have chronic disease.^{4,5} One must therefore be alert for asthma in the elderly population. When symptoms and signs are atypical and when response to standard therapy is suboptimal, however, one must be aware of a possible differential diagnosis. A careful examination of this patient would have revealed that the 'wheeze' was not audible at all on auscultation. The history of haemoptysis gave another clue. The flow-volume loop of this patient showed marked reduction of peak inspiratory and expiratory flow. The slope of the mid-expiratory limb was convex towards the volume axis. This is typical of intrathoracic upper airway obstruction and is due to the increased intrathoracic pressure on the intrathoracic airways during forced expiration. In extrathoracic airway obstruction, the airway is not affected by increased intrathoracic pressure at expiration. When obstruction is advanced, both inspiration and expiration flow is reduced, as in this patient. The flow-volume

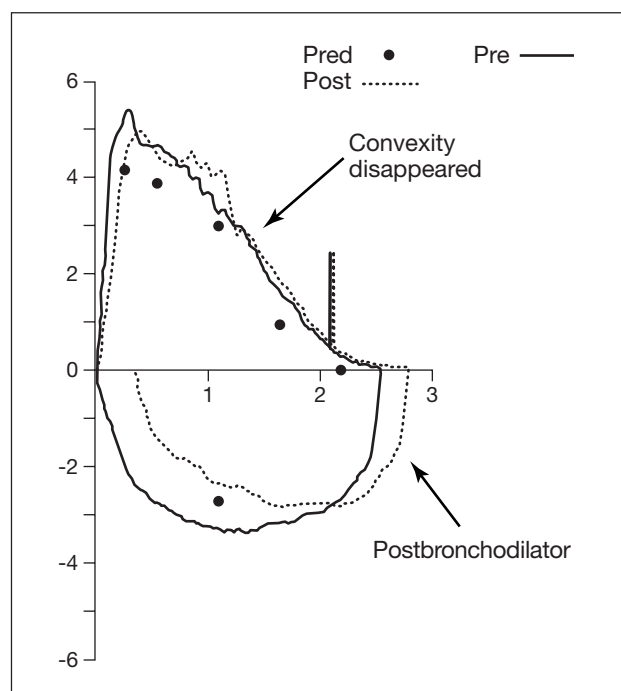


Fig 5. Flow-volume loop 11 months after diagnosis, and 9 months after chemotherapy and radiotherapy

loop at 11 months after diagnosis and treatment showed loss of the previous convexity towards the volume axis with improvement of both inspiration and expiration flow. The FEF₂₅₋₇₅ also showed marked recovery.

Lymphoepithelioma-like carcinoma of the lung

Lymphoepithelioma-like carcinoma of lung was first reported by Begin⁶ in an Asian patient. A total of 75 patients, including this patient, have been described to 2001. The largest series of 32 patients was reported by Han et al^{7,8} from China. This cancer is more common among Asians than Caucasians (67 versus 8). There is a high incidence of positivity for EBV demonstrated either by IgA VCA, polymerase chain reaction (PCR), or ISH for EBER among patients with LELC. This association of EBV only applies to Asians, however.⁹ The youngest reported patient was 9 years old,¹⁰ while the oldest was aged 78 years. This condition is more common among non-smokers. Most of these tumours are discovered at an early stage. The tumour tends to be relatively less invasive, with little metastasis, and patients have a long survival. The overall 2- and 5-year survival rates for pulmonary LELC are 79.9% and 53.5%, respectively, whereas for non-LELC pulmonary cancer, the rates are 53.5% and 39.1%, respectively. For stages II, III, and IV LELC, patients have a significantly better survival rate compared with patients with non-LELC pulmonary carcinoma. No significant difference in survival rate was observed between patients with stage I disease, however.⁸

Histology

Undifferentiated tumour cells intermixing with small lymphocytes is characteristic of LELC. The tumour cells

have pleomorphic oval vesicular nuclei and prominent nucleoli.¹¹ Similar to undifferentiated nasopharyngeal carcinoma (NPC), LELC is characterised by two main patterns. The Regaud type shows well-defined epithelial nests separated by broad areas of lymphocytic reaction. The Schmincke type shows tumour cells growing in a diffuse syncytial manner mimicking malignant lymphoma. The histology type does not affect survival.

Epstein-Barr virus infection in tumour can be demonstrated by VCA IgA, PCR, or ISH demonstrating EBER inside the tumour cells. Polymerase chain reaction is sufficiently sensitive to detect EBV in latently infected, non-neoplastic lymphocytes, and therefore does not specifically localise the virus to the tumour cells. In situ hybridisation against viral DNA can be applied to fixed paraffin sections, but is relatively insensitive. This technique is highly sensitive against EBER transcripts, which occur in large quantities in latently infected cells and it also enables cellular localisation. Sex, lymph node, or distant metastasis and clinical stage have no correlation with EBER expression.¹⁰ Epstein-Barr virus-associated lung cancers are not restricted to LELC, adenocarcinoma or squamous cell cancer of lung have also been known to exhibit EBER. The recent discovery of the EBV genome in tumour cells demonstrates that undifferentiated nasopharyngeal carcinoma, similar to endemic Burkitt's lymphoma, is a clonal expansion of a single EBV-infected cell.¹¹ Given the established linkage between EBV and undifferentiated nasopharyngeal carcinoma, a proportion of LELC may be associated with nasopharyngeal carcinoma. Nasopharyngeal examination and blind biopsy in this patient did not demonstrate any nasopharyngeal carcinoma. The VCA IgA was also negative but ISH demonstrated EBER in tumour cells.

Key points

The key points to this paper are that when a patient has persistent unrelieved wheezing, one must consider other causes

of airflow obstruction. When a wheeze is heard with the ears, but there are no rhonchi on auscultation, stridor should be excluded. Nasopharyngeal carcinoma should be excluded when LELC is detected especially among Asian patients.

Acknowledgement

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