JOURNAL OF FORENSIC SCIENCES

J Forensic Sci, January 2011, Vol. 56, No. 1
doi: 10.1111/j.1556-4029.2010.01546.x
Available online at: interscience.wiley.com

CASE REPORT

PATHOLOGY/BIOLOGY

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All that Wheezes is not Asthma—Alternative Findings at Autopsy

ABSTRACT: A number of questions must be asked before asthma can be accepted as a valid diagnosis: were the episodes of shortness of breath investigated? Are there changes at autopsy in keeping with asthma? Did asthma either contribute to the terminal episode, cause death, or was it coincidental? Finally, is it possible that other conditions may have accounted for the clinical manifestations? A review of files at FSSA over a 10-year period from 1999 to 2008 identified six cases where shortness of breath and/or wheezing had been incorrectly attributed to asthma. Five were due to pulmonary thromboembolism and one to multiple injuries. In the latter case, an irreducible, left-sided diaphragmatic hernia was present. There was no morphological evidence of asthma in any case. Autopsy examination may, therefore, be crucial in revealing other conditions that may have caused or contributed to episodic breathlessness that may have been incorrectly attributed to asthma.

KEYWORDS: forensic science, asthma, pulmonary thromboembolism, diaphragmatic hernia, misdiagnosis

The determination of a likely sequence of terminal events in an individual who has presented to autopsy is often guided by a careful integration of the pathological findings with the clinical history. A difficulty with this approach, however, is that it relies on the accuracy of antemortem diagnoses. While a number of studies have reported on clinical misdiagnoses of asthma (1), there is little information in the forensic literature on this topic. A study was therefore undertaken to examine the types of conditions that may be unexpectedly identified at autopsy due to an antemortem misdiagnosis of asthma because of episodic shortness of breath and/or wheezing.

Materials and Methods

The author's files at Forensic Science SA (FSSA) over a 10-year period from 1999 to 2008 were retrospectively searched for all cases where asthma was mentioned in the clinical history. Review of files was undertaken and those cases were selected where there was no macroscopic or microscopic evidence of asthma and where an alternative condition was identified that could cause transient episodes of dyspnea. At the same time a literature search (utilizing the United States National Library of Medicine "Entrez PubMed" database; http://www.ncbi.nlm.nih.gov/pubmed/) was conducted for reports detailing alternative conditions that may present as asthma.

Results

A total of six cases were identified where shortness of breath and/or wheezing had been incorrectly attributed to asthma. Five of the deaths were due to pulmonary thromboembolism and one to multiple injuries in a vehicle accident. In the latter case, a congenital diaphragmatic hernia was present. Given the nature of the material reviewed, population-based data could not be derived, however, the details of two representative cases have been provided to demonstrate features that may be identified at autopsy. As well, given the incomplete nature of coronial medical histories, it was not possible to provide a more accurate time line for the symptoms of shortness of breath. Additional conditions that have been reported in the literature that may mimic the clinical presentation of asthma are listed in Table 1.

Case 1

An obese 61-year-old man with intellectual disability following childhood head trauma and a past history of "asthma," was found dead in bed. His body mass index was 33.9. At autopsy, bilateral saddle pulmonary thromboemboli were identified in addition to multiple peripheral pulmonary thromboemboli. There were no pulmonary infarcts. In addition to recent pulmonary thromboemboli, microscopy also identified previous thromboembolism with organization and recanalization of pulmonary vessels (Fig. 1). There was also evidence of aspiration of gastric contents. No other significant organic diseases were present that could have caused or contributed to death. Specifically, there was no hyperinflation of the lungs, mucus plugging, eosinophilic infiltrate, basement membrane thickening or goblet cell hyperplasia to suggest asthma. There was also no evidence of trauma. Death was due to bilateral pulmonary thromboembolism.

The presence of previous pulmonary thromboemboli within the lungs in the absence of features of asthma suggested that previous episodes of shortness of breath were more likely to have been caused by pulmonary embolism rather than to bronchospasm related to asthma. Obesity may have predisposed to pulmonary thromboembolism and establishing the clinical diagnosis may have been complicated by the intellectual impairment of the deceased.

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Received 28 Aug. 2009; and in revised form 24 Oct. 2009; accepted 31 Oct. 2009.

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TABLE 1—*Conditions that may mimic asthma.*

Respiratory
Upper airway
Infection—retropharyngeal abscess, Ludwig angina, epiglottitis, laryngotracheobronchitis
Infiltrating diseases—Wegener granulomatosis, amyloidosis, sarcoidosis
Laryngeal stenosis
Vocal cord paralysis
Laryngotracheal tumors
Tracheal stenosis
Tracheo- and bronchomalacia
Foreign body impaction
Extrinsic compression—goiter, vascular ring, mediastinal tumor, innominate artery aneurysm, esophageal foreign body, achalasia
Lower airway
Chronic lung disease—cystic fibrosis, chronic obstructive airways disease, bronchopulmonary dysplasia
Endobronchial tumors
Pneumonia
Cardiovascular
Congestive cardiac failure
Pulmonary thromboembolism
Gastrointestinal
Aspiration syndromes
Congenital diaphragmatic hernia
Miscellaneous
Anaphylaxis

Case 2

A 34-year-old man with a past history of "asthma" and heroin addiction died after the vehicle that he was driving collided with a tree. At autopsy, there were significant injuries to the head, chest, and abdomen with a fractured base of skull with subarachnoid hemorrhage, atlanto-occipital joint instability, multiple bilateral rib fractures with laceration of the right lung and a right-sided hemothorax, anterior and posterior mediastinal hemorrhage, lacerations of the liver, and spleen with a hematoperitoneum, bruising of the mesentery, and laceration of the right kidney. In addition, there was a 55-mm-diameter left-sided diaphragmatic hernia associated with irreduceable herniation of 500 mm of large intestine (including the distal transverse colon, the splenic flexure, and the proximal descending colon) into the left chest cavity (Fig. 2). This was associated with collapse of the left lung that weighed only 387 g compared to the right lung that weighed 718 g. Microscopy revealed atelectasis of the left lung with diffuse areas of interstitial fibrosis. There was no evidence of asthma either macroscopically or microscopically. The edge of the diaphragmatic defect showed fibrosis with scattered hemosiderin-containing macrophages.

Toxicological evaluation of blood revealed the following levels: alcohol—0.014%, methadone—0.2 mg/L, diazepam—0.05 mg/L, alprazolam—0.2 mg/L and morphine—0.38 mg/L. Monoacetylmorphine was not detected in the urine. Although the levels of methadone and morphine were high, the effects may have been ameliorated by prior exposure with habituation. However, the combined defects of alcohol and drugs would have in all likelihood had a sedative effect, with impairment of motor reflexes. Death was attributed to blunt trauma involving the head, chest, and abdomen.

Subsequent review of the medical record showed that there had been no objective confirmation of the diagnosis of asthma. Although the deceased had been referred to a respiratory clinic at a tertiary hospital for assessment he had not kept the appointment. The presence of 500 mm of large intestine within the left pleural cavity with compression of the left lung, in the absence of features of asthma, suggested that previous episodes of shortness of breath were more likely to have resulted from pulmonary compression because of the diaphragmatic hernia rather than to bronchospasm.

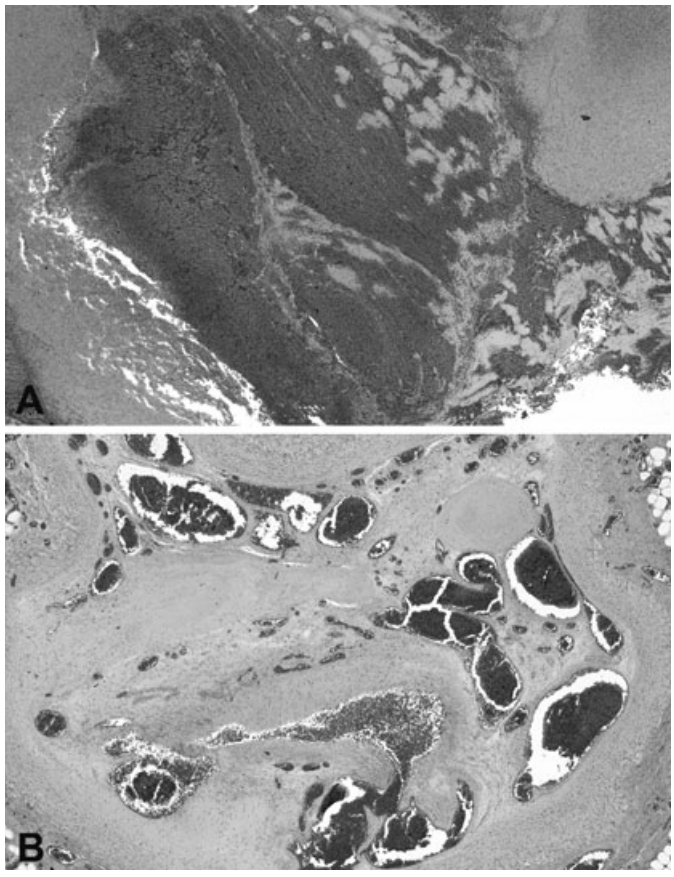

FIG. 1—*Recent pulmonary thromboembolism (A) and recanalized thromboemboli (B) in a 61-year-old man with a history of episodic shortness of breath that had been attributed to asthma (case 1) (Hematoxylin & eosin ×200).*

Discussion

Asthma is characterized by episodic shortness of breath with wheezing due to paroxysmal bronchospasm. It occurs at most ages and may be associated with quite rapid death due to status asthmaticus, or less often to the added complications of pneumothorax with lung collapse (2). While the clinical diagnosis is usually straightforward, the pathological findings may be less obvious, with variable macroscopic features of pulmonary hyperinflation and mucus plugging of airways, sometimes modified by attempted resuscitation. Similarly, the extent of basement membrane thickening, eosinophilic infiltrate, and goblet cell hyperplasia on histology does not always correlate with the severity of the clinical manifestations (3), i.e., relatively innocuous microscopic findings may be found in a witnessed asthmatic collapse and death, whereas more impressive features may be incidental findings in deaths because of unrelated causes. As in many situations determination of the possible role played by the autopsy findings requires careful clinicopathological correlation to ascertain whether the deceased died from, or merely with, asthma.

Histological changes of asthma may be encountered at autopsy in the absence of a clinical history. While this may be a reflection of the inadequacy of the medicolegal history, it is also possible that the manifestations of the underlying lung pathology were either

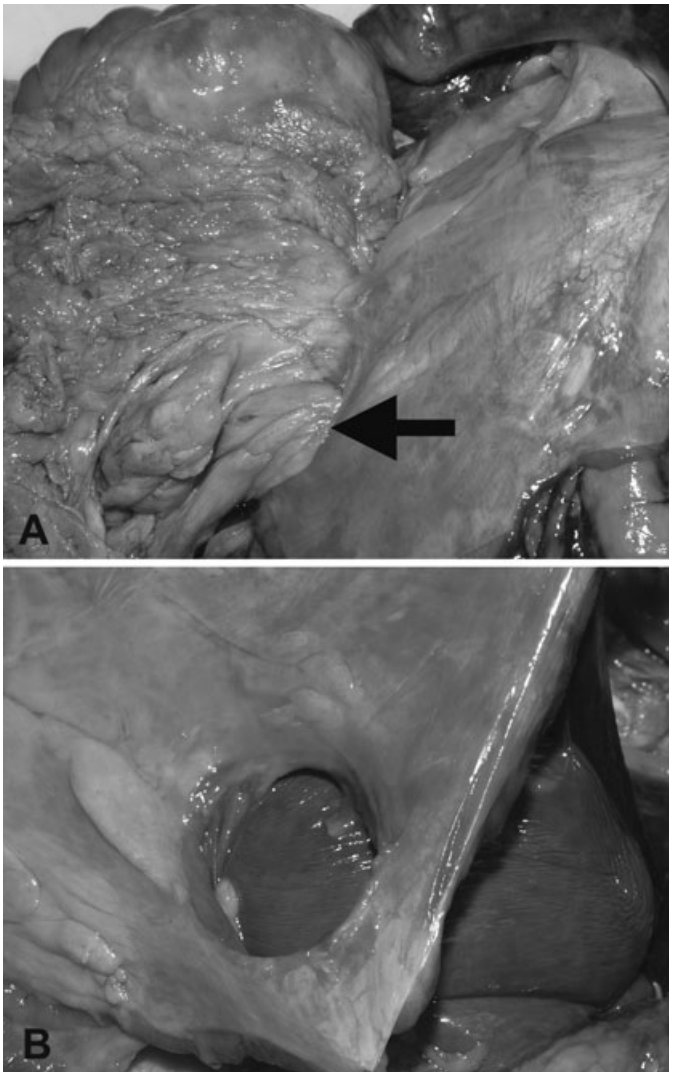

FIG. 2—*An irreduceable hernia of the colon into the left chest cavity (A) in a 34-year-old man with a history of episodic shortness of breath (case 2). Dissection of the colon away from the hernia revealed the 55-mm defect with the spleen beneath (B).*

minimal, or were ignored by the deceased. For example, underappreciation of the severity of asthma not uncommonly occurs in adolescents (2). The assessment of the seriousness of a medical condition may also be hampered when a patient is suffering from intellectual disability as in case 1. Even when a history of asthma is present, the histologic findings may range in severity from well-established changes of disease to normal lung parenchyma.

The current report has, however, focussed on another aspect of the autopsy and asthma, and that is of possible alternative entities that may have resulted in clinical misdiagnosis. The adage of "all that wheezes is not asthma" (1) could be extended to "all that causes episodic shortness of breath is not asthma," as there is a diverse range of conditions that may potentially be confused with asthma clinically.

Review of autopsy files is often complicated by complex and coincidental pathology. For example, individuals with asthma may develop ischemic heart disease later in life, and so it may be difficult to determine which condition predominated in the absence of a clear description of the terminal episode. For this reason when FSSA autopsy files were reviewed, only those cases where there was no macroscopic or microscopic evidence of asthma, with the presence of unequivocal alternative pathology, were included in the study. Given these parameters, the most common entity found at autopsy to have been misdiagnosed as asthma was pulmonary thromboembolism. While most pulmonary thromboemboli arose from the deep veins of the legs associated with risk factors of immobility, obesity, and neoplasia, thromboemboli resulting in episodic shortness of breath that may be confused with asthma may also arise from indwelling intravascular lines such as atrioventricular shunts in cases of hydrocephalus associated with Arnold-Chiari malformation, at any age (4,5). Showers of peripheral pulmonary thromboemboli may be sufficient in number to cause a ventilation-perfusion mismatch with resultant shortness of breath without resulting in overt infarction. Resolution of embolic vascular obstruction may then result in reduction in the severity of symptoms. Histologic evidence of this may be present in the form of recanalization of organized thrombi, as in case 1.

A rare cause of episodic reversible shortness of breath was also demonstrated in case 2 where 500 mm of colon had formed an irreducible hernia through a hiatus in the left dome of the diaphragm. Although unrelated to death, there had been a history of poorly investigated asthma that in all likelihood was related to the large intestinal herniation. Given the presence of fibrous scarring and hemosiderin staining at the edges of the hernial orifice, it is most likely that the diaphragmatic hernia was acquired following trauma, although this could not be confirmed on review of the rather scanty clinical record that was available. Thus, the possibility of a congenital diaphragmatic hernia was not excluded, as occasional cases persist into later adult life before manifesting themselves (6,7). Congenital diaphragmatic hernias have rarely been reported as a cause of wheezing (8,9), although this has been predominantly in childhood. It is of interest that there was a history of heroin use in this case, as heroin and cocaine used have been associated with inducing fatal and near-fatal episodes of asthma (10,11). The underlying mechanism may involve mast cell degranulation. However, as there was no macroscopic or histologic evidence of asthma this appears not to have played a role in the terminal episode.

Thus, when a history of "asthma" is noted in the clinical record at autopsy with minimal supportive clinical evidence it is perhaps preferable to replace the word "asthma" with "episodic shortness of breath," or "alleged asthma" as these terms may be a more accurate reflection of the situation and allow for other possibilities to be considered. Even in individuals with well-established diagnoses of asthma, the possibility of alternative pathology involving a range of other organ systems that may cause episodic breathlessness should be considered (1,2) (Table 1).

Acknowledgment

I thank the South Australian State Coroner, Mr. Mark Johns, for permission to report selected details of these cases.

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