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Pediatric Pulmonary Hemorrhage vs. Extrapulmonary Bleeding in the Differential Diagnosis of Hemoptysis

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Abstract

Introduction: Hemoptysis is an important symptom which causes a major concern, and warrants immediate diagnostic attention. The authors compared a group of patients with pediatric pulmonary hemorrhage with pediatric patients diagnosed with extrapulmonary bleeding focusing on differences in etiology, outcome and differential diagnosis of hemoptysis.

Methods: We performed the retrospective analysis of medical charts of 134 pediatric patients admitted to the Emergency Department because of pulmonary and extrapulmonary hemorrhage and were diagnosed with suspected hemoptysis or developed hemoptysis (ICD10-CM code R04.2). The cases with pulmonary hemorrhage (Group 1) were compared with cases of extrapulmonary bleeding (Group 2) using the Fisher Exact test or Pearson's χ^2 test for categorical variables. The t-test was used to assess differences between continuous variables of the patients in the two groups.

Results: Bloody cough was the presenting symptom in 73.9% of cases. 30 patients had pulmonary hemorrhage (Group 1), while 104 patients had extrapulmonary bleeding (Group 2). The underlying causes of bleeding in Group 2 included epistaxis, inflammatory diseases of nasopharynx and larynx, foreign bodies, gingivitis, and hypertrophy of adenoids. Mortality rate was 10% in Group 1, whereas Group 2 did not have any mortality outcomes during the observation period. Etiologycal factors were significantly different between hemoptysis and extrapulmonary bleeding in children

Conclusions: Our research suggested that pulmonary and extrapulmonary bleeding are two conditions that differ significantly and cannot be unified under one diagnostic code. It is important to differentiate between focal and diffuse cases, and between pulmonary and extrapulmonary hemorrhage due to the diversity of clinical courses and outcomes.

Keywords: *Pulmonary Hemorrhage; Extrapulmonary Bleeding; Hemoptysis, Epistaxis; Pediatric*

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Research

Hemoptysis is an important symptom which causes major concern in both patients and physicians, and warrants immediate diagnostic attention. The incidence of pediatric hemoptysis in the general population is not well established because hemoptysis is a symptom associated with numerous diseases and no special symptom-related epidemiological report has been published so far. As a result, hemoptysis is a term with numerous definitions that only partially overlap with each other. The narrowest medical dictionary definition describes hemoptysis as the expectoration of blood-tinged sputum derived from the lungs or bronchial tubes as a result of pulmonary or bronchial hemorrhage.[1]

Hemoptysis is a rare symptom in children.[2] Since children tend to swallow their sputum, bloody sputum may go unnoticed unless it is substantial.[3] Hemoptysis in adults is most often caused by bronchitis, tumors, tuberculosis or bronchiectasis.[4,5] However,

among the pediatric population, blood-tinged sputum is most likely to be secondary to infection, foreign body aspiration, or tracheostomy related problems.[2,6,7] In 1990s, cystic fibrosis and congenital heart diseases (mitral stenosis) were reported as predominant etiologic factors for hemoptysis.[8] Currently, various etiologies are suggested including idiopathic pulmonary hemosiderosis, pulmonary vascular malformation, pulmonary arteriovenous fistula, bronchiectasis, pulmonary tuberculosis, and lung tumors, with cystic fibrosis accounting for only 5% of cases.[9]

Extrapulmonary bleeding, sometimes referred as pseudohemoptysis, is a common umbrella term for all types of hemorrhage not derived from the lungs or bronchial tubes and excluding hematemesis. Since both pulmonary and extrapulmonary types of bleeding can be dangerous and sometimes life-threatening, physicians require adequate knowledge in this area in order to provide rapid and effective interventions.

While the above definition of hemoptysis clearly localizes the lower respiratory tract as the place of origin of the pathology, this restriction is not always taken into account in the clinical practice. Emerging literature included "upper airway bleeding" and "pharyngitis"[10] as well as "nasopharyngeal bleeding"[11] to describe the etiology of hemoptysis. These inclusions might be based on wider definitions of hemoptysis as "the expectoration from the respiratory tract of both blood-streaked sputum and gross blood"[12] or "coughing up blood as a result of bleeding from the respiratory tract."[13] Finally, hemoptysis is sometimes defined as just "the expectoration of blood or blood-tinged sputum."[2] This definition is the most inaccurate because it mixes hemoptysis and hematemesis. The differential diagnosis between hemoptysis and hematemesis is relatively simple starting from alkaline or acidic pH of the blood-containing sputum. The difference was well described recently,[11,14] but it seems that differential diagnosis between hemoptysis/pulmonary hemorrhage and extrapulmonary bleeding requires further clarification.

Previously published literature suggests that "hemoptysis is rare in children and adolescents"[15,16], which highlights the gap in the literature that this paper will attempt to address. The purpose of this study was to review 14 years of experience with hemoptysis and extrapulmonary bleeding among children in a secondary medical center. We will also compare the frequencies of diagnostic presentations between pediatric pulmonary hemorrhage and extrapulmonary bleeding with an emphasis on etiology, clinical course, outcome and differential diagnosis between them, as well as analyzing possible correlations between patents' personal characteristics and etiology of the bleeding. In the present article, the term "hemoptysis" is used as "the expectoration of blood-tinged sputum derived from the lungs or bronchial tubes as a result of pulmonary or bronchial hemorrhage", and the importance of the proper definition is addressed further in the Discussion section.

Methods

Participants

Institutional review board approval was obtained for this study from Assaf HaRofeh Medical Center Ethical Board (Helsinki Registration #225-09). The authors conducted a retrospective chart review of pediatric patients, aged 1-18, who were admitted to Pediatric Intensive Care Unit, Ear, Nose, and Throat-Head and Neck Surgery Department, and Pediatric Surgery Department, Assaf HaRofeh Medical Center, Israel, because of suspected hemoptysis or developed hemoptysis (ICD10-CM code R04.2) between January 2004 and December 2016. Charts of the patients who were hospitalized and who were discharged from the Emergency Department were analyzed according to the inclusion criteria. The analysis focused on identifying similarities/differences in the general data (age, sex, number of cases), etiology, symptoms, clinical and laboratory findings, and outcomes that might be important for differential diagnosis.

Variables	Pulmonary bleeding	Extrapulmonary bleeding	p
General			
N	22.4% (n=30)	77.6% (n=104)	0.02*
M/F	16/14	56/48	0.44*
Median age, years	7.6	5.1	0.03**
Diagnostic findings			
Bloody cough	73.3% (n=22)	74% (n=77)	0.9*
Diffuse lung infiltrations	53.3% (n=16)	10.6% (n=11)	0.02*
Focal pathology in lungs	60% (n=18)	0%	<0.01*
Positive sputum cultures	13.3% (n=4)	0%	<0.01*
Positive blood cultures	6.7% (n=2)	0%	<0.01*
Foreign body	16.5% (n=5)	11.54% (n=12)	0.05*
Symptomatic anemia	33% (n=10)	8.7% (n=9)	0.03*
Management			
Antibiotic treatment	60% (n=18)	35.6% (n=37)	0.03*
Mechanical respiratory support	33% (n=10)	0%	<0.01*
Packed cell transfusion	33% (n=10)	8.7% (n=9)	0.02*
Outcome			
Cessation of the hemorrhage	80% (n=24)	100% (n=104)	0.07*
Surgery or transfer	10% (n=3)	0%	<0.01*
Mortality rate	10% (n=3)	0%	<0.01*

*p-values were calculated using Chi square or Fisher's test
** p-values were calculated using t-test

Table 1. Comparison between patients with pulmonary and extrapulmonary bleeding.

Patients were identified using the hospital computerized database and were categorized into two groups: Group 1, which included patients with confirmed hemoptysis as a result of pulmonary or bronchial hemorrhage; and Group 2, which included patients with extrapulmonary bleeding.

The main inclusion criterion for charts was the presence of complete and detailed data that would be sufficient for differential diagnosis. These included detailed health history, clinical data with adequate description of respiratory or hemodynamic symptoms, chest radiography, and bronchoscopy and/or direct laryngoscopy or nasopharyngoscopy. Data on microbiology, serology (including serology for vasculitis) and chest computed tomography (CT), were also analyzed. Exclusion criteria were iatrogenic bleeding, hematemesis, cases with trauma that caused both internal and external bleeding, and incomplete data in the charts.

Etiology	Extrapulmonary (n=104)	Pulmonary bleeding (n=30)	p*
Infections/inflammations	55 (53%)	15 (50%)	0.87
Foreign body	12 (11.54%)	5 (16.7%)	0.05
Tonsils/adenoids hypertrophy	10 (9.6%)	0 (0%)	<0.01
Bronchiectasis	0 (0%)	5 (16.7%)	<0.01
Vascular malformation	0 (0%)	2 (6.7%)	<0.01
Idiopathic/traumatic epistaxis	23 (22%)	0 (0%)	<0.01
Massive aspiration	0 (0%)	2 (6.7%)	<0.01
Toxic effect (cocaine)	0 (0%)	1 (3.3%)	-
Severe cough of unknown origin	4 (3.87%)	0 (0%)	<0.01

*p-values were calculated using Chi square or Fisher's test

Table 2. Etiology of hemoptysis and extrapulmonary bleeding in children.

Statistical analysis

Descriptive statistics were used to describe the basic data trends. Cases with pulmonary hemorrhage were compared with cases of extrapulmonary bleeding using the Fisher's Exact test or Pearson's χ^2 test for categorical variables (gender, diagnostic findings, management, outcome) and t-test for continuous variable (age). The Pearson correlation coefficient was calculated to detect possible connections between analyzed variables and gender and age of the patients. The data were analysed using SPSS, Standard version 17.0 (SPSS, Chicago, IL, 2007). The level of significance for all analyses was set at $P<0.05$.

Results

Over the course of 12 years of observation134 pediatric patients with suspected hemoptysis were admitted to the Medical Center Emergency Department (0.2% of all pediatric admissions to the Emergency Department). Of them, 86 (64.2%) were hospitalized for 24 hours or more. The patients had a median age of 5.6 years (range 0.15-17), with no difference between genders (p=0.86). Bloody cough was the presenting symptom in 73.9% (n=99), the remainder later developed a non-cough related hemorrhage. Further hospital investigation revealed that 30 out of 134 patients (22.4%) presented with expectoration of blood-tinged sputum as a result of pulmonary or bronchial hemorrhage, while the rest had extrapulmonary bleeding (p=0.02). All patients underwent an otolaryngology evaluation including endoscopy/nasopharyngoscopy that excluded or confirmed upper airway sources of bleeding. In all analyzed patient records, the routine blood-containing sputum pH test was performed to rule out hematemesis. Chest radiographs were important for classifying diffuse or focal disease, with diffuse pulmonary hemorrhage being a more severe condition (Fig. 1A). Bronchoscopy was performed mostly in cases with focal signs detected on a chest X-ray images in order to explore the source

Pt	Chest Imaging	Bronchoscopy
1.	Bronchiectasis RML and lingual	Normal
2.	Bronchial wall thickening RML & lingual	
3.	LLL consolidation	Normal
4.	RUL consolidation and cavitations	Partially obstructed main bronchus RUL
5.	Diffuse infiltrates	
6.	LLL Infiltrates	Normal
7.	Diffuse alveolar infiltrates	Normal
8.	RUL and LLL pneumonia	
9.	Diffuse infiltrates	Was not performed because of suffocation
10.	Bilateral basal infiltrates	
11.	Bilateral infiltrates	
12.	Mild RLL infiltrates	Foreign body
13.	Right diffuse infiltrates	Foreign body
14.	RLL atelectasis	Foreign body
15.	Bilateral infiltrates	
16.	Bronchiectasis RML	Normal
17.	RUL and LLL pneumonia	
18.	Right diffuse infiltrates	Foreign body
19.	Bronchial wall thickening RML	
20.	LLL Infiltrates	Normal
21.	Diffuse infiltrates	
22.	RLL infiltrates	Foreign body
23.	Non-calcified nodule	Normal
24.	LLL Infiltrates	Normal
25.	RML consolidation and cavitations	Obstructed main bronchus RML
26.	Bronchial wall thickening RML, RLL	
27.	Bronchiectasis RML	
28.	Bronchial wall thickening RUL	Bronchopneumonia
29.	Bronchiectasis RUL, infiltrates	
30.	Consolidation area in the LSL	Normal

Abbreviations: LLL, left lower lobe; LSL, left superior lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe

Table 3. Chest imaging and bronchoscopy of the patients with pulmonary hemorrhage.

and cause of bleeding, and when foreign body aspiration was suspected.

The characteristics and comparison between patients with pulmonary and extrapulmonary bleeding is presented in the Tables 1 and 2.

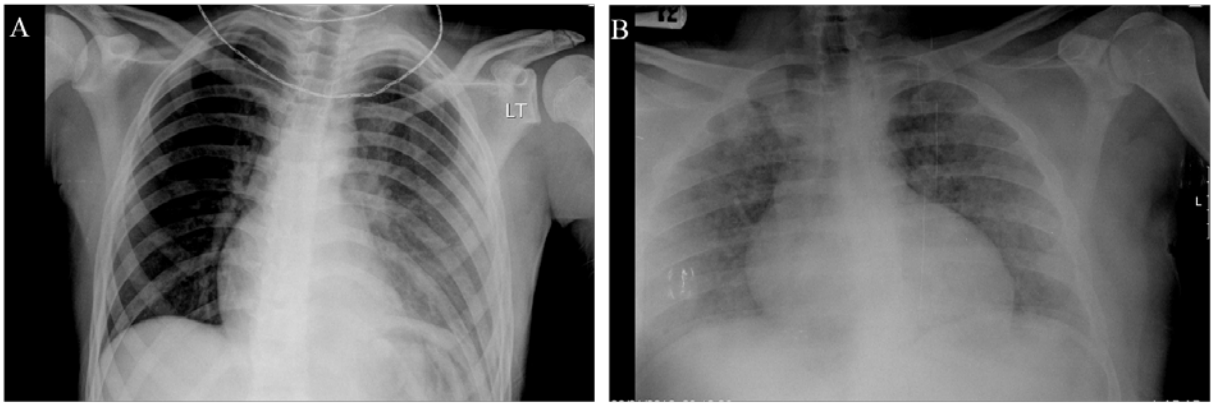

Figure 1. (A) Radiographic picture of a case of hemoptysis as a result of left lower lobe pneumonia due to mycoplasma; (B) A case of cocaine induced pulmonary hemorrhage. Chest-X ray and CT scan showed bilateral micronodular opacities.

Pulmonary hemorrhage.

Among the patients with pulmonary hemorrhage (n=30, mean age 7.6), infection or foreign body aspiration were the leading etiological causes of focal pulmonary hemorrhage. All five patients with foreign body aspiration presented themselves more than 24 hours following the suspected aspiration event. Twelve patients with bleeding of pulmonary or bronchial origin (40%) had an underlying pathology (Table 3). Coagulation function tests and cell blood count were abnormal in four patients, one of them with severe gram negative sepsis and the other three with severe coagulopathy due to fulminant hepatic failure. Cardiac evaluation, including echocardiography, was performed in 25 patients (those with foreign body aspiration were excluded) and revealed a small atrial septal defect in one case, and mild pulmonary hypertension in another case. Gram negative sepsis was found in one patient and candida sepsis in another patient, while the remaining patients had negative blood cultures. The cases with positive sputum cultures (n=4) revealed mycoplasma, mycobacteria, and pseudomonas. Serology for mycoplasma (IgG and IgM) was positive in one patient. Other serology tests such as antinuclear antibodies and antineutrophil cytoplasmic antibodies and complement factors were obtained and found to be within the normal range in 18 patients. While urinalysis excluded renal pathology in all patients, urine toxicology screening indicated one case that was positive for cocaine.

A positive bronchoscopic finding was observed in eight patients with focal findings and hemoptysis as a result of pulmonary or bronchial hemorrhage, comprising 44.5% of the patients in whom bronchoscopy was performed. Data on chest imaging and bronchoscopy of the patients with hemoptysis are presented in the Table 3.

Infectious bronchopneumonia was diagnosed in nine patients (30%). CT diagnosed bronchiectasis in six patients (20% of pulmonary hemorrhage cases, 4.5% of all cases). The sweat test for cystic fibrosis was uninformative. All patients (n=10) who required mechanical respiratory support had diffuse lung infiltrates.

Complete cessation of the hemoptysis was observed in 24 patients during their hospitalization period (80%), 22 of them achieving complete radiological and clinical resolution within four weeks. The death of three patients (10%) occurred because of

severe sepsis and liver failure, all diagnosed with diffuse pulmonary hemorrhage. Three patients were transferred to other institutions for surgical treatment and treatment of tuberculosis; their long-term outcomes are not known. The overall outcome of the remaining patients with confirmed pulmonary hemorrhage was good during a follow up period of 6-18 months (median 9 months) with complete resolution of symptoms.

Extrapulmonary hemorrhage.

The group of patients with extrapulmonary bleeding (n=104, mean age 5.1 years) differed in terms of the presentation and the resolution of the disease. Infection or foreign body in upper airways and epistaxis (ICD10-CM code R04.0) were the leading etiological causes of hemorrhage. In this group, all 12 patients with foreign bodies presented during the first 12 hours following the suspected event. Endoscopy and nasopharyngoscopy data were essential for the diagnostic process in all cases. Serology tests such as antinuclear antibodies and antineutrophil cytoplasmic antibodies and complement factors were obtained and found to be within the normal range in 26 patients.

In this group, complete cessation of the hemorrhage was observed in all patients during their hospitalization period. A follow up period of 6-18 months (median nine months) indicated no recurrent episodes.

Correlation data

No correlation was found between the gender of the patients and etiology of the bleeding and diagnostic findings (r=0.21 and r=0.32 respectively). The positive correlation with younger age (less than six years old) was found for the presence of a foreign body at any location from nasopharynx and larynx to esophagus and bronchi (r=0.83) and idiopathic/traumatic epistaxis (r=0.65). The massive aspiration was detected only in the pulmonary cases.

Discussion

Diagnostic code ICD-10-CM R04.2 defines hemoptysis as coughing or spitting up blood from the respiratory tract with further clarification as “expectoration or spitting of blood originating from any part of the respiratory tract, usually from hemorrhage in the lung parenchyma (pulmonary alveoli) and the bronchial arteries.” Our research suggested (Tables 1 and 2) that pulmonary and extrapulmonary bleeding are two conditions that differ significantly and cannot be unified under one diagnostic code. In our series of extrapulmonary bleeding cases, there were 23 (22%) patients with idiopathic or traumatic epistaxis that should be encoded as ICD10-CM code R04.0. In pediatric cases; however, some blood often proceeds to nasopharynx and then presents itself as bloody sputum or cough that can mislead a practitioner in correct codification.

Proper definition for hemoptysis poses both, a research/policy problem and a clinical practice challenge. Pediatric patients with extrapulmonary bleeding may be referred to the departments of otorhinolaryngology or maxillo-facial surgery, while patients with pulmonary or bronchial hemorrhage are to be admitted to Pediatric Intensive Care Unit and/or the department of pediatric surgery. In our studies, bloody cough was the presenting symptom in 74% of cases. Therefore, the “coughing up blood” definition is not entirely correct and further clarification of definition for hemoptysis is desirable. For example, the most recent study of Simon et al. reported prevalence rates for the most common causes of hemoptysis in pediatric cases and identified pneumonia, bronchitis, and pulmonary tuberculosis as the most common specific etiologies.[17] In this case, the authors used the term “hemoptysis” only in refernce to pulmonary or bronchial hemorrhage.

Extrapulmonary bleeding very rarely leads to mortality. Our cases with mortality were related mostly to the underlying disease (hepatic failure, sepsis and acute respiratory distress syndrome (ARDS)) and less to the degree of pulmonary hemorrhage. Patients with poor

prognosis that have been described in the literature mainly present with diffuse pulmonary hemorrhage in a context of autoimmune pulmonary-renal syndrome,[18] which is a combination of glomerulonephritis with bleeding in the lungs and is very rare among the pediatric population.[19] However, we had no cases with renal pathology in our study.

A foreign body aspiration is a specific pediatric problem especially in infancy and early childhood. In our study, all the participants with foreign body aspiration had positive radiological findings, a fact that can be explained by their late referral. However, chest radiographs may be normal in the first 24 hours following foreign body aspiration. The presence of atelectasis, pulmonary infiltrates, and a mediastinal shift suggest foreign body aspiration.[20]

Since cystic fibrosis is the most likely cause of bronchiectasis in children, it was ruled out in these patients. Efrati et al. described a similar incidence (9%) of hemoptysis among Israeli children with bronchiectasis due to cystic fibrosis, 12.5% of them requiring bronchial artery embolization.[21]

Hematologic bleeding diseases are rarely associated with hemoptysis and pulmonary hemorrhage in children.[19] In the current study, 14% of the patients with pulmonary hemorrhage suffered from significant coagulopathy due to hepatic failure or sepsis. The two patients with hepatic failure did not undergo a liver transplant due to a high grade of hepatic encephalopathy on admission; therefore, the high percentage of pulmonary hemorrhage and mortality in these patients is explained by the natural course of their liver disease.

Cocaine abuse was found to be the cause of anemia, diffuse pulmonary hemorrhage, and respiratory failure in one of our patients (Fig. 1B). Such case is rare but similar cases were previously reported describing an acute anemia associated with an alveolar hemorrhage after inhalation of cocaine.[22,23] The pathogenesis is not clear yet but an opinion was expressed that cocaine-induced vasoconstriction, vascular damage in the lung tissue, platelet activation, and procoagulatory activity could lead to such pathology.

Hemoptysis related to bacterial, viral, and fungal pulmonary infections was previously described.[24-26] We confirmed that such patients may have lobar lung infiltrates, concomitant leukocytosis, and high C-reactive protein. A study on 21 symptomatic patients with asthma revealed hemoptysis in 29% of them.[27] Our single asthmatic patient presented infiltrates in the middle lobe and lingual suggesting the middle lobe syndrome. Congenital vascular malformations are relatively rare and we only had two such cases. However, these malformations can remain unnoticed for a long time. Recently, a case was described with a 10-month history of recurrent hemoptysis due to unilateral absence of the pulmonary artery.[28]

Within extrapulmonary cases, laryngeal trauma seems to be the most life-threatening cause of bleeding because the direct clinical symptoms rarely correlate with the degree of respiratory tract failure.[29] The idea that incidence of extrapulmonary bleeding is significantly higher than pulmonary hemorrhage calls to attention to these cases and to the differential diagnosis process between pulmonary and extrapulmonary hemorrhage.

Our results demonstrate that the differential diagnostics between extrapulmonary and intrapulmonary bleeding may be based on significant differences of median age, frequency, clinical time-course of foreign-body aspiration, diffuse infiltration of chest X-ray images, and prevalence of severe anemia between the two groups. We believe that for pediatric emegency of this nature, whatever initial suspicion of a physician on duty might be, both a pediatric pulmonologist and a pediatric otorhinolaryngologist should be invited for consultation. Pediatricians may appreciate the fact that in the majority of cases the expectoration of blood-tinged sputum has nothing to do with lung diseases. At the same time, pediatric ENT specialists should be well prepared

to evaluate patient for a serious pulmonary disorder in cases of such expectoration.

While our study was limited to pediatric cases, we must point out that while extrapulmonary and intrapulmonary bleeding can occur at any age, the pediatric cases differ from adult cases and warrant further research. For example, the presence of a foreign body in the respiratory tract is a very common pediatric problem while the lung tumor is extremely rare in children and adolescents. Another limitation is that our medical center is a large university-affiliated general hospital that does not provide pediatric cardiac surgery, transplantation, or cystic fibrosis services. This could be the reason why patients with these conditions, typically associated with bleeding, were not found in the present study.

While extrapulmonary hemorrhage is the main etiology for bloody cough in most of the developed countries, developing countries may have other experiences with this condition. There are countries where pediatric cases of tuberculosis are common. Reports from Tunisia, Turkey, and Iran indicate a need to provide a differential diagnosis between cases of tuberculosis and asthma (pulmonary source of hemorrhage) in contrast to allergic rhinitis (extrapulmonary source of hemorrhage).[30-32] Also, while cystic fibrosis is no longer considered the main cause of hemoptysis in Israel, this may not be the same in other countries.[33] Development of the most precise differential diagnosis between pulmonary and extrapulmonary hemorrhage remains an acute necessity for improvements in public health in many countries of the world.

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