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EDITORIAL

Clinical asthma phenotyping: A trial for bridging gaps in asthma management

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Abstract

Asthma is a common disease affecting millions of people worldwide and exerting an enormous strain on health resources in many countries. Evidence is increasing that asthma is unlikely to be a single disease but rather a series of complex, overlapping individual diseases or phenotypes, each defined by its unique interaction between genetic and environmental factors. Asthma phenotypes were initially focused on combinations of clinical characteristics, but they are now evolving to link pathophysiological mechanism to subtypes of asthma. Better characterization of those phenotypes is expected to be most useful for allocating asthma therapies. This article reviews different published researches in terms of unbiased approaches to phenotype asthma and emphasizes how the phenotyping exercise is an important step towards proper asthma treatment. It is structured into three sections; the heterogeneity of asthma, the impact of asthma heterogeneity on asthma management and different trials for phenotyping asthma.

Key words: Asthma phenotypes; Asthma heterogenity; Endotypes; Asthma subtypes; Asthma syndrome

Core tip: Although asthma diagnosis is based mainly on clinical basis using history taking and physical examination, treatment options are not tailored according to the clinical phenotype. We still do not have a way to work up a given patient with asthma and to easily delineate the specific pathobiology that leads to her or his airway dysfunction. We can recognize the clinical syndromes, but we cannot spell out the steps that lead from genetic or biochemical defects to disease presentation. Thus we are left with a paradox in the study of asthma; we have effective treatments that are not biologically informative, and we have informative treatments that are less effective.

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INTRODUCTION

Asthma is a chronic inflammatory airway disease characterized by episodic reversible airway obstruction that variably presents with cough, wheezing, shortness of breath, or chest tightness[1,2].

Asthma affects nearly 300 million people worldwide. Moreover, western countries have shown rising prevalence over the past three decades[2]. The prevalence of bronchial asthma in the Nile Delta region of Egypt was found to be 7.7%[3].

Asthma is a heterogeneous and genetically determined disease with different presentation, disease progression, and response to therapy. However, despite this recognition, the treatment approaches for asthma have been uniformly applied irrespective of its "subtype"[4]. Guidelines advocate a universal stepwise approach in which medications are initially prescribed based on patient age and asthma severity, and then the number, frequency, and dose of medications are titrated upward when asthma control is inadequate.

The fact that there are some asthmatic patients with variable presentations who do not respond to commonly used medications and classified as severe asthma[5,6], has driven the urgent need to phenotype the disease using unbiased approaches, and depending mainly on essential clinical and physiologic features for better treatment approaches.

Different researches have tried to shape asthma phenotypes through their clinical, physiologic and cellular parameters. A phenotype was defined as "observable characteristics" of subtypes of asthma ranging from clinical presentation, triggering factors to therapeutic responses. While, the fact of asthma pathogenesis is far beyond that as these different asthma phenotypes are based on different underlying biologic processes in each patient[7].

For better understanding of this heterogeneity and the complexity of clinical and research results, the term "endotype" was evolved reflecting a specific pathogenic mechanism. Endotype was defined according to molecular pathogenesis or therapeutic responses. Thus, accurate identification of those asthma endotypes could help in tailoring of asthma therapy[2].

ASTHMA AS A HETEROGENEOUS DISEASE

Heterogeneity of asthma reflects different clinical presentations with different responses to asthma medicines. This makes a challenge for the appropriate choice of asthma treatment. Thus, a better understanding of this heterogeneity could be of great help. Asthma heterogeneity could be explained at four levels: clinical, biological, therapeutic and molecular levels (Table 1).

Clinical level

Different studies suggest phenotypic classification of asthma depending on clinical basis. These phenotypes include allergic and non allergic asthma. Other phenotypes defined by clinical or physiological categories (*i.e.,* severity, age at onset, and chronic airway obstruction), by asthma triggers (*i.e.,* viral, exercise, occupational allergens, or irritants), or their course (*i.e.,* early transient/persistent/late onset wheeze) have also been proposed[8]. Other asthma phenotypes include cough variant asthma and obese asthma phenotype. Cough variant asthma was recognized as an asthma phenotype that solely presents with coughing[9]. This asthma phenotype was defined by the presence of atopic features, milder eosinophilic airway inflammation and airway remodeling[10].

Obese asthma phenotype is assumed to be non T helper type 2 (Th2) mediated in which low fractional exhaled nitric oxide, eosinophils and IgE levels were observed[11,12]. Preliminary studies have suggested that in late onset obese asthma, there is increased asymmetric dimethylarginine which inhibits inducible nitric oxide synthetase leading to superoxide generation increasing the oxidative stress in such patients[13].

Biological level

The heterogeneity of asthma as an inflammatory disorder is well established. Simpson *et al*[14] have detected specific inflammatory endotypes in sputum samples consistent with cytokine profiles in asthmatic patients forming different endotypes that ranged from: eosinophilic, neutrophilic, mixed, and paucigranuloctic subtypes[15]. Severe asthma was found to be a different disease entity dating since birth with a specific underlying biology[16,17]. Thus, it should be viewed like this rather than the end result of airway remodeling. Recently, Zedan *et al*[18] correlated clinical asthma phenotypes with the underlying cytokine and genetic pattern. Serum cytokines levels were found to be a reflection of cytokine gene polymorphisms *via* affecting the transcriptional regulation. The clinical asthma phenotypes showed statistically significant differences in cytokine profile and genotyping distribution of IL4RA-175V and IL4C-590T. Further a different genotyping was noticed when dealing with asthma as a group and after its clinical phenotyping.

Therapeutic level

In spite of asthma heterogeneity, the prescribed medications for asthma management are similar involving B2 agonists, leukotriene receptors antagonists and inhaled corticosteroids. These asthma medicines were found to control the symptoms in the majority of patients and failed in others. Several researches tried to explain this variable response to asthma therapy in different patients.

The polymorphism of β2 receptors could adversely affect the response to regular short-acting drugs[19]. On the other aspect, 15% of asthmatics show a reasonable response to leukotriene modifiers. However, polymorphism in 5 lipoxygenase (ALOX) and the

Table 1 Examples of proposed clinical phenotypes

	Clinical level	Clinical characteristics	Biological level	Molecular level	Therapeutic level
Xie *et al*[2]	Exercise induced asthma	Mild asthma and reactive bronchospasm in response to sustained exercise	Mast-cell activation; Th2 cytokines; cysteinyl leukotrienes		Responsive to cysteinyl leukotriene modifiers, beta agonists and antibody to IL-9
	Obesity asthma phenotype	Adult onset Mostly females Severe symptoms	Lack of Th2 biomarkers; oxidative stress ADMA		Responsive to weight loss, antioxidants and possibly to hormonal therapy
	Early-onset Allergic asthma	> 3 episodes per year Mild, moderate, or severe Family history of asthma	Specific IgE; Th2 cytokines; thick SBM	17q12; Th2-related genes	Corticosteroid-responsive; Th2-targeted
	Late-onset Eosinophic asthma	Adult onset Often severe Sinus disease	Increased both peripheral eosinophils and IL-5		Responsive to antibody to IL-5 and cysteinyl leukotriene modifiers; corticosteroid-refractory
Zedan *et al*[8]	Shortness of breath phenotype	> 10 yr No sex predominance Longer disease duration Negative family history of asthma	Increased total serum IgE	Higher prevalence of TT genotype of SNP IL-4C 590T (Zedan *et al*[18])	Responsive to fluticasone alone
	Cough phenotype	< 10 yr Female predominance Shorter disease duration Positive family history of asthma	Increased both peripheral eosinophis and sECP		Responsive to montelukast alone
	Wheezy phenotype		Increase in peripheral eosinophilis and sECP		Responsive to both fluticasone and montelukast

ADMA: Asymmetric dimethyl arginine; SBM: Subepithelial basement membrane; SNP: Single nucleotide polymorphism; sECP: Serum eosinophilic cationic protein; IL: Interleukin; Th2: T helper type 2.

receptor (CYSLTR2) were found to affect the drug response[20,21].

Further, differences in corticosteroid responsiveness may be caused by complex genetic variations as more than 100 genes were found to be involved in allergic asthma, but these genetics variations are influenced by environmental exposures. Moreover, in many cases, it has been difficult to establish clear linkage because of disease heterogeneity and poorly stratified populations[22].

By stratifying patients according to phenotype, future studies may be better able to identify the genes or other biomarkers associated with various aspects of asthma. Currently, the use of specific biomarkers to diagnose and monitor asthma is in its infancy but is being evaluated in clinical trials[23].

Molecular level

Despite the importance of Th2 cytokines in atopic asthma, recent data in both adults and children has challenged the concept of a Th1/Th2 imbalance and has showed an evidence of Th1 profile.

Th2 imprint was present in only 50% of the mild asthmatics and those patients were characterized by lung eosinophils, mast cells, higher IgE levels, hyperreactive airway, higher tissue expression of Th2 cytokines and thicker subepithelial basement membrane[24,25]. In addition, they showed a good response to inhaled corticosteroids in contrast to those without the type-2 cytokine profile.

IMPACT OF ASTHMA HETEROGENEITY ON ASTHMA MANAGEMENT

Asthma therapy can markedly improve quality of life, morbidity, and mortality of asthma patients and decrease health care costs if applied to the right patient at the right time[26]. The choice of controller medications should be based on clinical efficacy, patient phenotype, previous responses to treatment, patient's compliance, side effects, and drug safety[27].

Although asthma diagnosis is based mainly on clinical basis using history taking and physical examination[28], treatment options are not tailored according to the clinical phenotype. We still do not have a way to work up a given patient with asthma and to easily delineate the specific pathobiology that leads to her or his airway dysfunction. We can recognize the clinical syndromes, but we cannot spell out the steps that lead from genetic or biochemical defects to disease presentation. Thus we are challenged by a paradox in the management of asthma; we have effective treatments that are not biologically informative, and we have informative treatments that are less effective[29].

Recently, the new emerging cytokine based therapies flare the importance of asthma phenotyping. Effective application of these new therapies to certain patients depends on the development of biomarkers of

molecular heterogeneity in asthma[30].

DIFFERENT TRIALS FOR ASTHMA PHENOTYPING

A phenotype is defined as the "observable properties of an organism that are produced by the interactions of the genotype and the environment"[31]. Multiple approaches have been proposed for asthma phenotyping, none has been widely agreed upon. Many of those approaches have been biased; depends mainly on clinical characteristics without obvious inflammatory biomarkers. Also, the selection of a single dominant characteristic to categorize a given patient is mostly inaccurate as it ignores the overlap between groups[32]. These include categorization of patients based upon atopic state, symptomatic trigger, disease severity, and pattern of airflow obstruction. In addition, pathological classifications, despite being important for clarifying disease pathogenesis, they are extremely invasive clinically.

Several studies have approached asthma phenotyping in a less biased and more statistically based manner[31] as a result of lacking of specific biomarkers for each asthma phenotype. Three large clinically oriented analyses performed in Europe[33,34] and the United States[35,36] developed clusters based upon age of onset of asthma, gender, allergic features, asthma symptoms, and lung function as well as other factors that varied between the three studies. The resulting phenotypes include early-onset mild allergic asthma, later-onset asthma associated with obesity, and severe non-atopic asthma with frequent exacerbations.

Four clusters were identified based upon asthma duration, the number of asthma controller medications, baseline Forced Expiratory Volume in 1 s, skin test, and total serum IgE. All of them were strongly associated with histories of atopic dermatitis and atopy, although the degree of atopy as measured by number of positive allergy skin tests and total serum IgE did differ significantly between groups[34]. However, these studies lacked the accurate pathological and immunological definition of asthma phenotypes[31].

Asthma has a strong genetic component[37]. Most of genetic association studies have dealed with asthma as a one disease[38] and only few studies[39] delineated specific asthma phenotypes. Asthma subtypes cannot be termed phenotypes without linking the observable characteristics to the genetic signature of the patients[40]. Woodruff *et al*[41] began to identify molecular phenotypes of asthma. They analyzed airway epithelial brushings and they identified "TH2 high" and "TH2 low" individuals.

Zedan *et al*[27] proposed three clinical asthma phenotypes based on symptomatology after validation of these symptoms[42,43]. The study tried to characterize three clinical phenotypes [shortness of breath (SOB), cough, and wheeze] by specific inflammatory biomarkers and their response to asthma medications. They found that children who had SOB had older age, and longer disease duration, higher levels of total serum IgE, and responded to fluticasone alone. While cough group was found to have younger age, shorter disease duration, higher levels of eosinophilic% and serum Eosinophilic Cationic Protein, and responded to montelukast alone. Moreover, wheezy group showed mixed pattern and responded to both medications[27].

Two single nucleotide polymorphisms (SNPs) in IL-4 and IL4RA were studied in Egyptian asthmatics with different clinical phenotypes[18]. They found that asthma as a group had AG heterozygosity genotype, whereas cough with SOB group showed AA and GG homozygosity genotype. In addition, cough group and SOB group revealed significant increase in serum levels of IL-17 among patients with CC homozygote variant of IL-4C 590T compared to patients with CT heterozygote variant. In turn, phenotyping based on symptomatology makes a sense in endotyping of asthma, which may have a reflection on heterogeneity in response to asthma medications[18].

The previously mentioned clinical asthma phenotypes were found to express a significant value in detection of specific cytokine and genotype profiles for asthma; hence this may help in prediction and diagnosis of clinical asthma phenotypes which might have a potential value in tailoring asthma therapies.

The concept of personalized medicine, however, gained most traction from the application of genetics to patients with disease. Polymorphisms in genes (both single nucleotide polymorphisms, SNPs, and other more substantive coding variations) are associated with therapeutic responses to short-acting beta2 agonists, leukotriene inhibitors, corticosteroids, and several others; other polymorphisms confer risk of developing diseases: asthma, atopy, bronchial hyperresponsiveness, *etc*[44].

CONCLUSION

Asthma is a complex disease with evidenced heterogeneity at different levels. Despite this heterogeneous nature, the same treatment approaches are still applied for different patients with variable responses. Phenotyping/endotyping dilemma is the only roadmap to bridge the gap between this variable disease and the single approach of management. A key obstacle in this field is a lack of "gold standard" phenotypes with underlying identifiable biomarkers, genetic, or molecular profiles. A novel conceptual framework to link the clinical signature of every patient to her/his inflammatory phenotype is very essential to meet the challenges of tailoring the right medications for to the right patient at the right time.

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MINIREVIEWS

Appendicitis in children less than five years old: A challenge for the general practitioner

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Abstract

Acute appendicitis is one of the most common indications for abdominal surgery in pediatrics with peak incidence in the second decade of life. Acute appendicitis in the first years of life is an uncommon event. The clinical presentation is often varied and the diagnosis may be overshadowed by other medical conditions. Gastroenteritis is the most common misdiagnosis, with a history of diarrhea present in 33% to 41% of patients. Pain is the most common presenting symptom in children less than 5 years old, followed by vomiting, fever, anorexia and diarrhea. The most common physical sign is focal tenderness (61% of the patients) followed by guarding (55%), diffuse tenderness (39%), rebound (32%), and mass (6%). Neonatal appendicitis is a very rare disease with high mortality; presenting symptoms are nonspecific with abdominal distension representing the main clinical presentation. The younger the patient, the earlier perforation occurs: 70% of patients less than 3 years develop a perforation within 48 h of onset of symptoms. A timely diagnosis reduces the risk of complications. We highlight the epidemiology, pathophysiology, clinical signs and laboratory clues of appendicitis in young children and suggest an algorithm for early diagnosis.

Key words: Appendicitis; Children; Early diagnosis; Newborn; Appendicitis complications

Core tip: Acute appendicitis in the first years of life is an uncommon event but with a high incidence of early perforation the younger the patient. We highlight the epidemiology, pathophysiology, clinical signs, and laboratory clues of appendicitis in young children. The challenge for the practitioner is to perform a timely diagnosis of acute appendicitis in first years of life before complications occur.

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INTRODUCTION

Acute appendicitis has the highest incidence during the second decade of life[1], and represents a frequent indication for abdominal surgery in pediatrics[2]. It is more common in males than in females (ratio 1.4:1)[2]. While up to 33% of affected children may present not distinct abdominal pain with consecutive pain localization in the right lower quadrant, nausea and vomiting, young children could show atypical or delayed symptoms presentation[3-5]. When the diagnosis is performed, perforation could be already present in 30%-75% of children, with young children being at higher risk[6]. Perforated appendicitis increases the morbidity with intra-abdominal abscess being an important complication[7]. In young children, appendicitis is an uncommon event with a varied presentation and complications that can develop rapidly[8,9]. A timely diagnosis although necessary can be difficult, representing a challenge for the physician.

EPIDEMIOLOGY

In a study over a 12-year period, 1836 pediatric appendectomies were reviewed. Three hundred and twenty (17%) patients were under 5 years of age, 103 (5%) were less than 3 years, with only 7 patients (0.38%) younger than 1 year[7]. Perforation was more frequent in young children (the perforation rate was 86% in children less than 1 year of age, 74% between 1 and 1.9 years, 60% between 2 and 2.9 years, 64% between 3 and 3.9 years, and 49% between 4 and 4.9 years), while the rate in older patients was 5%[7]. Seven patients under 1 year of age were included so that the statistical relevance of the differences in the perforation rate of the different age groups would be limited[7]. Moreover, male patients present more risk of perforation than female patients also if the symptoms have a similar duration[10].

A single pediatric center study over a 28-year period reported a similar rate of appendicitis in patients under 1 year of age (0.34%) and 2.3% in patients under 3 years[11].

Andersen *et al*[9], in a cohort of Danish children, reported an annual incidence of 2.22/10000 among boys less than 4 years and 1.82/10000 among girls less than 4 years with a perforation rate of 0.64 and 0.62, respectively. The annual incidence among 10-19 years old boys and girls was 22/10000 and 18/10000 respectively, with a perforation rate of one third the rate of young children[9].

The risk of perforation increases with diagnostic delay. In children 5-12 years old, if the diagnosis is made in less than 24 h from the outbreak of symptoms, the reported perforation rate is 7%, if between 24-48 h 38%, and if more than 48 h 98%[8]. In patients < 3 years, the perforation rate is high (70%), even if the time to diagnosis is less than 48 h[4].

A timely diagnosis is more difficult in toddlers because of presentation to emergency department delayed since the outbreak of symptoms of 1.6 d for patients less than 5 years[7], and 3 d in patients less than 3 years[11].

ANATOMIC AND PATHOPHYSIOLOGIC ELEMENTS

Differences in the appendicitis clinical presentation could be explained by age-related variations in appendiceal anatomy and development. In the neonatal period, the appendix is 4.5 cm long reaching the length of 9.5 cm in adults[12]. Acute appendicitis is rare in neonates because they present a funnel-shaped appendix[13,14], have liquid diet, supine posture, low frequency of gastrointestinal and upper respiratory tract infections[15]. Furthermore, there is evidence that breast-feeding could reduce the risk of appendicitis[16].

Between 1-2 years of age, the appendix becomes similar to that of an adult and the susceptibility to inflammation increases. Lymphoid follicle hyperplasia and follicular size gradually increase with the major expression during adolescence, corresponding to the period of the highest rate of appendicitis[1]. Young children have an undeveloped omentum that is not able to limit the purulent material effusion from a perforation[17]. For this reason, diffuse peritonitis following a perforation is more likely in young children[18]. The mobility of fetal and infant appendices is accentuated and the probability of appendix to be fixed by mesenteric connections to the cecum, ascending colon, or abdominal wall is lower[19]. This could explain why the incidence of localized abscesses in young children is infrequent.

HISTORY AND CLINICAL EXAMINATION

In preverbal toddlers and preschoolers, the anamnesis about the pain is difficult to examine[20]. In preverbal children, clinicians need to relay on the physical examination and on detecting contingent signs of pathology evaluating how children eat, move around, play, sleep, and defecate[20]. Many children, in particular young children, can be easily influenced. Even though their conflicting significances, questions such as "Does it hurt here?" and "This feels fine, right?" may lead to the same positive answer[20]. Abdominal pain usually begins as vague mid-abdominal or periumbilical pain migrating to the right lower quadrant during an interval of hours to days, and many school-aged children can accurately report and localize their pain movement. However, young children may not be able to describe accurately their symptoms, and the clinicians could locate the pain exclusively asking the children to show the painful abdominal point[20].

Pain is the most frequent presenting symptom in children less than 5 years old. In a cohort of 120 patients less than 5 years, 94% presented with pain,

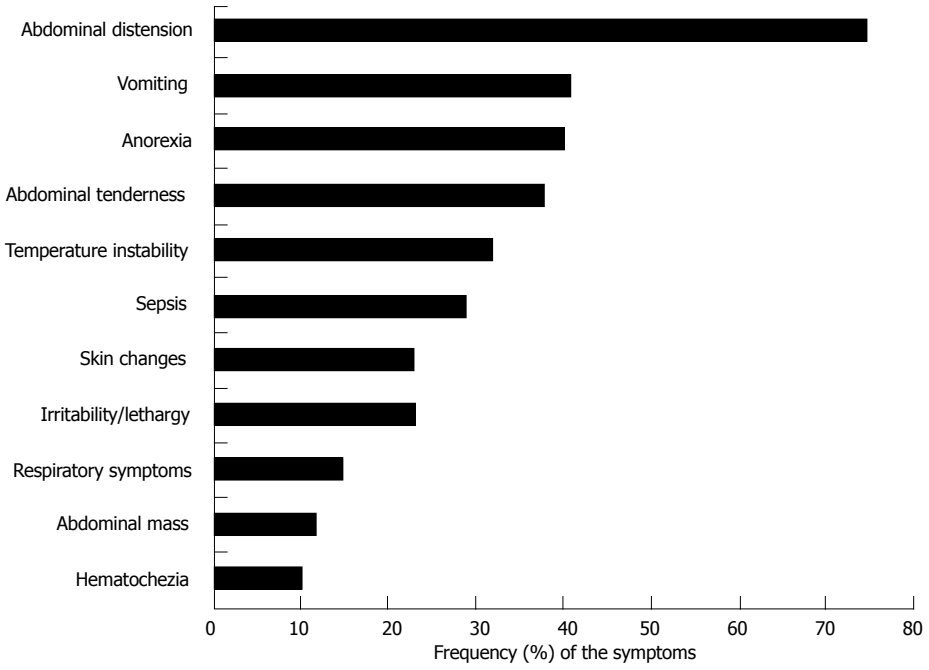

Figure 1 Neonatal appendicitis: frequency of symptoms at presentation (modified from ref.[24]).

83% with vomiting, 80% with fever, 74% with refusal to eat, and 32% with diarrhea[21]. When the data was restricted to children less than 3 years, vomiting, fever and diarrhea were more frequent[11]. If the appendicitis is non-perforated the most common physical sign is localized tenderness (61%) followed by guarding (55%), diffuse tenderness (39%), rebound (32%), and mass (6%)[21]. If the appendicitis is perforated, the most frequent sign is the guarding (79%) followed by diffuse tenderness (62%), rebound (39%), localized tenderness (33%), mass (9%), and rigidity (7%)[21].

In the neonatal period, the signs and symptoms are nonspecific with irritability or lethargy (22%), abdominal distension (60%-90%), and vomiting (59%)[15,22]. Other symptoms include a palpable mass (20%-40%)[15], abdominal wall cellulitis (12%-16%), hypotension, hypothermia, and respiratory distress[22-25]. The most common clinical presenting signs and symptoms are reported in Figure 1[24].

LABORATORY EVALUATION

White blood cell count (WBC) and C-reactive protein (CRP) are commonly used when an acute appendicitis is suspected. Conventional WBC count presents both low sensitivity and specificity, in fact it could increase in 70% of the patients presenting abdominal pain for causes different from appendicitis[26]. A high WBC count or a left shift (represented by higher than 80% polymorphonuclear cells along with bands) has good sensitivity (79%), while the coexistence of both positive WBC count and left shift present the greatest specificity (94%)[27]. The sensitivity and specificity of WBC counts range from 70%-80% and 60%-68%, respectively[28]. Up to 20% of children with pathologically proven appendicitis present a WBC in the normal range[29], while the leukocyte response declines in children younger than 5 years old with appendicitis[30].

CRP is more specific than WBC count, even if in the early stage of acute appendicitis the sensitivity is lower[26,31]. The reported sensitivity and specificity are of 57% and 87% respectively[28]. CRP presents higher sensitivity in discovering appendiceal perforation and abscess formation[26,31]. Recently, it has been demonstrated that the use of both WBC count and CRP may lead to enhanced negative predictive value[6,32]. Yokoyama *et al*[33] showed as indicative of surgical intervention a CRP cut-off value of 4.95 mg/dL (sensitivity 84% and specificity 76%). Procalcitonin is not helpful in the acute appendicitis diagnosis presenting a diagnostic accuracy lower than CRP and WBC[31]. When a complicated appendicitis is present the pooled procalcitonin sensitivity and specificity are 62% and 94%, respectively[31].

RADIOLOGICAL EVALUATION

Computed tomography (CT) has been considered the radiological gold standard to confirm clinical suspicion of appendicitis with high sensitivity and specificity[34,35]. Repeated CT carries an established risk of increased incidence of cancer in children and its use should therefore be limited to clear indications with a well-defined risk to benefit ratio[36]. Less operator dependence, easier visualization of retrocecal appendix, less interference of bowel gas, obesity, or patient pain and tenderness with image quality are included among CT advantages. For these reasons, CT remains the most common primary imaging method before

Table 1 Conditions mimicking childhood and neonatal appendicitis (modified from ref.[8])

Condition	Diagnostic clues
Gastroenteritis	Continuous abdominal pain
	Poor clinical condition with mild or no dehydration, continuous, focal abdominal pain, and lack of movement in infants and young children distinguishes appendicitis from gastroenteritis
	Acute appendicitis is more common during viral epidemics and bacterial gastroenteritis[44]
Upper respiratory tract infection[1]	The presence of concomitant signs of upper respiratory infection are common in toddlers and does not rule out the possibility of appendicitis
Pneumonia	Basal pneumonia may mimic appendicitis pain[45]
	Simultaneous pneumococcal pneumonia and appendicitis is well reported in the literature[46]
Sepsis	An acute appendicitis should be suspected and ruled out in any case of sepsis associated with abdominal pain and or abdominal tenderness[47]
Urinary tract infection	Peritoneal inflammation may cause voiding disturbances and bladder symptoms[48]
Blunt abdominal trauma	Acute appendicitis may be associated with blunt abdominal trauma[49-51]
Intussception	Abdominal US is highly operator dependent
	In presence of fever, localized pain and guarding in infants and young children, appendicitis should be ruled out[52]
NEC	With a history of NEC outside prematurity and signs of abdominal cellulitis, neonatal appendicitis should be ruled out[53]

[1]Includes diagnoses of otitis media, sinusitis, pharyngitis and upper respiratory tract infection. US: Ultrasonography; NEC: Necrotizing enterocolitis.

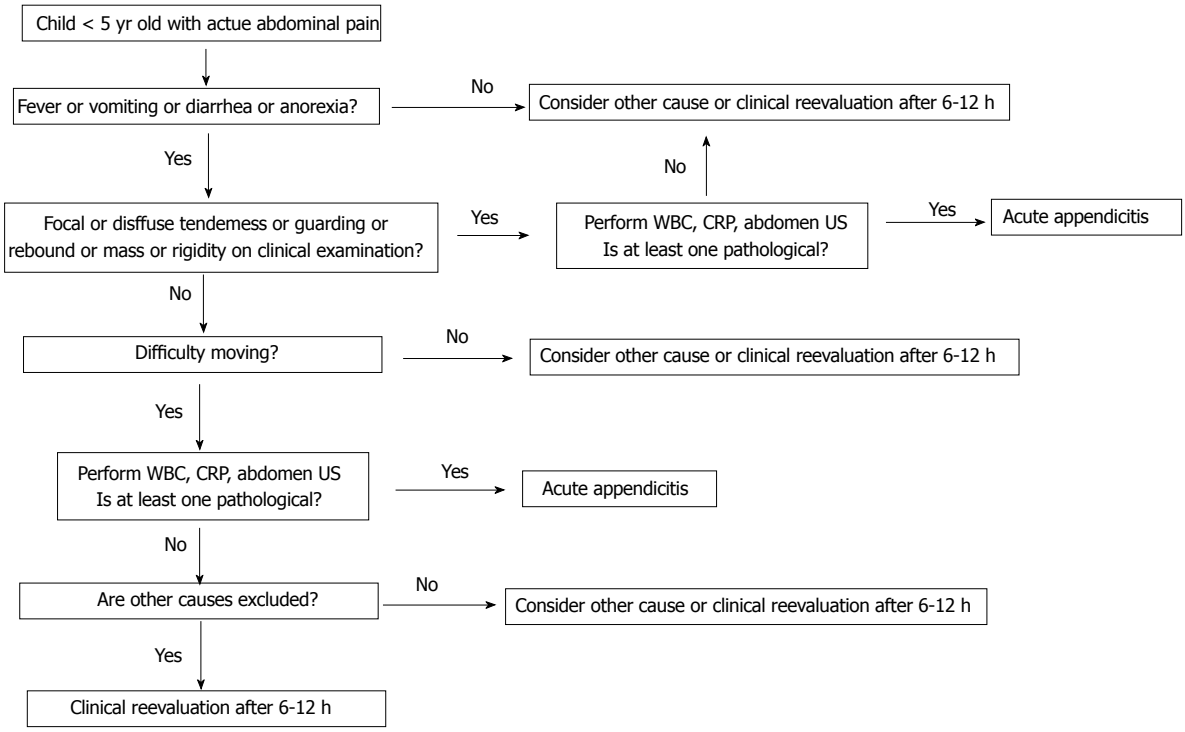

Figure 2 Diagnostic algorithm to assess acute appendicitis in young children. WBC: White blood cell count; CRP: C-reactive protein; US: Ultrasonography.

appendectomy in children[25,37]. To increase sensitivity of diagnosis but decrease radiation exposure, CT used in conjunction with equivocal ultrasonography (US) has been recommended as the most judicious diagnostic imaging pathway[38].

Using US for the acute appendicitis diagnosis is convenient and safe, but is highly operator dependent with a wide reported sensitivity range (44%-100%)[34,36,39]. There is evidence that the diagnostic accuracy can be improved[40] using specific US criteria and using repeated scans[41].

Magnetic resonance imaging (MRI) may also be used in young children[42]. Diagnostic imaging with US selectively followed by MRI is possible and comparable to CT, without differences in time to antibiotic administration and appendectomy, negative appendectomy and perforation rate, or length of stay[43]. Aspelund *et al*[43] showed an high US-MRI pathway specificity (99%) with a sensibility of 100%.

DIFFERENTIAL DIAGNOSIS

Appendicitis in young children is a diagnostic challenge. In a case series of 27 children less than 3 years, 67% had been visited by one or more clinicians without the diagnosis of acute appendicitis had been performed[11].

At this age the diagnosis of appendicitis may be hided by other medical conditions (Table 1). Gastroenteritis is the most common misdiagnosis (possible red flags to suspect appendicitis mimicking a gastroenteritis are shown in Table 1), in fact diarrhea may be present in 33%-41% of patients[4,26]. Importantly, as prior infective diseases may play a role in the physiopathology of acute appendicitis[54], diagnosis of a gastrointestinal, respiratory or urinary infection, should not rule out concomitant acute appendicitis[55].

CONCLUSION

A timely diagnosis of acute appendicitis in young children is a challenge due to the rarity of the disease, the varied presentation, and the rapid development of complications. A high level of suspicion and the knowledge of specific red flags can increase diagnostic skill. We present a diagnostic algorithm (Figure 2) that could be used to assess acute appendicitis in young children, optimizing diagnostic sources and limiting the CT use.

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MINIREVIEWS

Pyuria in patients with Kawasaki disease

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Abstract

Kawasaki disease (KD) is an acute, febrile vasculitis that predominantly develops in children ≤ 5 years of age and can lead to multiple organ injuries including the kidneys. Of these injuries, pyuria is a common feature of patients with KD, occurring in 30%-80% of patients. Sterile pyuria is most common in KD patients ≤ 1 year of age. KD patients with sterile pyuria exhibit more severe inflammatory reactions and may have sub-clinical renal injuries. Sterile pyuria in KD is associated with mononuclear cells (not neutrophils) in the urine. Although sterile pyuria in KD was at one time thought to be due to urethritis caused by a non-specific vasculitis of the urethra, recent studies suggest that sterile pyuria in KD originates from the urethra, the kidney as a result of mild and sub-clinical renal injuries, and/or the bladder due to cystitis. Pyuria is not always sterile in KD, but can result from a urinary tract infection (UTI). As causative pathogens, *Escherichia coli* and *Klebsiella oxytoca* have been reported. The clinical phenotypes do not differ between those with or without UTI. Because some KD patients with UTIs have urinary tract abnormalities such as vesicoureteral reflux, a complete UTI workup including renal ultrasound, voiding cystourethrogram and/or dimercaptosuccinic acid renal scan recommended in KD patients with UTIs.

Key words: Sterile pyuria; Kidney involvement; Urinary tract infection; Kawasaki disease; Vasculitis

Core tip: Pyuria is a common feature of patients with Kawasaki disease (KD), occurring in 30%-80% of patients. KD patients with pyuria exhibit more severe inflammatory reactions and may have sub-clinical renal injuries. Pyuria in KD originates from the urethra, the kidney as a result of mild and sub-clinical renal injuries, and/or the bladder due to cystitis. Pyuria is not always sterile in KD, but can result from a urinary tract infection (UTI). Because some KD patients with UTIs have urinary tract abnormalities, a complete UTI workup including renal ultrasound, voiding cystourethrogram and/or dimercaptosuccinic acid renal scan is recommended in KD patients with UTIs.

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INTRODUCTION

Kawasaki disease (KD) is an acute, febrile vasculitis that predominantly develops in children ≤ 5 years

of age[1]. KD affects medium-sized arteries, with a striking predilection for the coronary arteries[1,2]. Children with KD have an acute onset of fever, followed by signs of mucosal inflammation and vasodilation that evolve during the first week of the illness[1]. Laboratory examinations revealed a marked systemic inflammatory response[3]. The cause of KD remains unknown, but it is thought that the immune system is activated by infectious or environmental triggers in genetically-susceptible hosts[2,3].

Because KD is a systemic vasculitis, KD can involve multiple organs and tissues[2], including the coronary arteries, heart, joints, liver, central nervous system[4], muscle[5], and kidney[6,7].

Renal manifestations in KD includes pyuria, pre-renal acute kidney injury (AKI), renal AKI caused by tubulointerstitial nephritis, hemolytic uremic syndrome, immune-complex-mediated nephropathy, renal AKI-associated with KD shock syndrome, acute nephritic syndrome, nephrotic syndrome, and renal tubular abnormalities[7]. Of these renal manifestations of KD, pyuria is the most common abnormal finding[7]. Some KD patients with pyuria have been misdiagnosed with acute pyelonephritis[8], especially in cases of patients with incomplete KD[9,10], defined as patients with fever ⩾ 5 d but only 2 or 3 of the other KD criteria[2]. The following is a review of the prevalence, clinical and laboratory characteristics, and origin of pyuria in patients with KD.

PREVALENCE OF STERILE PYURIA IN PATIENTS WITH KD

No patients had pyuria according to the first report of KD, as described by Kawasaki[11] in 1967. Yamamoto *et al*[12] first described sterile pyuria in Japanese patients with KD in 1968. Yamamoto *et al*[12] reported that 8 of 23 (34.8%) patients with KD exhibited pyuria. Subsequently, Kawasaki *et al*[13] reported an increase in urine sediment leukocytes as a significant finding of KD in 1974. Thereafter, several studies regarding pyuria in KD have been reported. Melish *et al*[14] reported that 10 of 16 (62.5%) American patients with KD exhibited sterile pyuria. Barone *et al*[15] indicated that 13 of 27 (48.1%) American patients with classic KD and 4 of 11 (36.4%) patients with atypical KD had pyuria. Wirojanan *et al*[16] found that 23 of 70 (33%) Thai patients with KD had sterile pyuria. We also reported that 10 of 23 (43.5%) Japanese patients with KD had sterile pyuria[17]. Perrin *et al*[18] showed that pyuria was present in 45.3% of French patients with complete KD and in 30.8% of patients with incomplete KD. Recent studies by Shike *et al*[19], Sepahi *et al*[20], Liu *et al*[21], Choi *et al*[22], and Soleimani *et al*[23] have described sterile pyuria in 106 of 135 (79.8%), 32 of 47 (68%), 44 of 145 (30.3%), 40 of 133 (30%), and 17 of 47 (36.2%) patients with KD, respectively. Taken together, 30%-80% of patients with KD had pyuria (Table 1).

Table 1 The prevalence of pyuria in patients with Kawasaki disease

Ref.	No. of patients with pyuria /No. of total patients	The percent of patients with pyuria
Yamamoto *et al*[12]	8/23	34.8
Melish *et al*[14]	10/16	62.5
Barone *et al*[15]	13/27	48.1
Wirojanan *et al*[16]	23/70	33
Watanabe *et al*[17]	10/23	43.5
Perrin *et al*[18]		45.4
Shike *et al*[19]	106/135	79.8
Sepahi *et al*[20]	32/47	68.1
Liu *et al*[21]	44/145	30.3
Choi *et al*[22]	40/133	30
Soleimani *et al*[23]	17/47	36.2

In contrast, Turner *et al*[24] reported that 43% of febrile children without urinary tract infection had moderate pyuria (10-100 cells/high-power field) with only 9% of febrile children having definite pyuria (> 100 cells/high-power field). This finding indicated that pyuria might be a non-specific feature of fever in acute childhood illness. Shike *et al*[19] also reported that 79% of KD patients and 54% of febrile control subjects had sterile pyuria; however, they showed that the median urine white blood cell count was significantly higher in patients with KD than in febrile control subjects. Our study also showed that one-third of patients with KD exhibited definite pyuria[17]; thus, pyuria is a common feature of KD.

CLINICAL AND LABORATORY CHARACTERISTICS OF KD PATIENTS WITH STERILE PYURIA

Pyuria is defined as > 5 leukocytes/high-power field[25] or > 10 leukocytes/μL[26]. Sterile pyuria is defined as pyuria with a negative urine culture[26]. Sterile pyuria can occur in various infectious or noninfectious disorders (Table 2)[25,27]. Although pyuria can occur in patients with KD of all ages, pyuria is more common in patients ⩽ 1 year of age. Wirojanan *et al*[16] reported that 10 of 13 (77%) KD patients ⩽ 1 year of age had pyuria, although only 13 of 57 (22%) KD patients ⩾ 1 year exhibited pyuria. Liu *et al*[21] also reported that pyuria was present in 28 of 75 (40%) and 16 of 80 (20%) KD patients ⩽ 1 and ⩾ 1 year of age, respectively.

We studied the laboratory data of patients with KD divided into three groups: patients without pyuria, patients with pyuria in both voided urine and bladder urine obtained by transurethral catheterization (bladder pyuria), and patients with pyuria only in voided urine (urethral pyuria) and reported that the urinary protein level was higher in patients with pyuria than patients without pyuria, and the urinary β2-

Table 2 Causes of sterile pyuria in children

Causes
Infectious causes
Partially treated bacterial UTI
UTI in the presence of urinary obstruction
Renal tuberculosis
Renal abscess
Renal tuberculosis
Inflammation near the ureter or bladder (appendicitis, Crohn disease)
Febrile disorders other than UTI
Noninfectious causes
Nephrolithiasis
Kidney and urinary tract anomalies
Glomerulonephritis
Interstitial nephritis
Systemic lupus erythematosus
Interstitial cystitis
Kawasaki disease

UTI: Urinary tract infection.

microglobulin (β2MG), serum blood urea nitrogen (BUN) and creatinine levels were higher in patients with bladder pyuria than in patients with urethral pyuria or in patients without pyuria[17]. Choi *et al*[22] reported that the erythrocyte sedimentation rate, C-reactive protein level and serum concentrations of alanine aminotransferase and BUN were significantly higher in patients with pyuria than in patients without pyuria. These studies suggest that KD patients with pyuria exhibit more severe inflammatory reactions and may have sub-clinical renal injuries.

ORIGIN OF PYURIA IN PATIENTS WITH KD

Sterile pyuria in KD is associated with mononuclear cells (not neutrophils) in the urine[28,29]. A previous study demonstrated mononuclear cells with intracytoplasmic inclusions in the urinary sediment of a patient with KD, which might be derived from mononuclear phagocytic cells[30].

Sterile pyuria in KD was thought to be due to urethritis caused by a non-specific vasculitis of the urethra[29]. Melish *et al*[14] performed bladder taps on 4 KD patients with pyuria in voided urine specimens and reported bladder urine to be free of white blood cells, suggesting that urethral inflammation was the source of pyuria in patients with KD; however, we reported that 5 of 10 KD patients with sterile pyuria in voided urine samples also had leukocytes in bladder urine, suggesting that some patients with KD develop sterile pyuria that originates from the urethra and/or the kidney as a result of mild and sub-clinical renal injuries[17]. Renal injuries in patients with KD have been reported using imaging studies and/or urinary cytokines analysis. Ohta *et al*[28] reported that increased levels of urinary interleukin-6 (IL-6), β2MG and N-acetyl-β-D-glucosaminidase in most patients with KD. Wang *et al*[31] performed dimercaptosuccinic acid (DMSA) renal SPECT on 50 patients with KD, and reported that 26 of these patients (52%) had renal inflammatory foci. Wu *et al*[32] performed DMSA renal SPECT and renal Doppler ultrasonography to measure the pulsatility index (PI), and analyzed urinary IL-6 levels in 50 patients with KD. They showed that 10 of 24 (42%) patients had renal inflammatory foci, that patients with renal inflammatory foci had significantly higher levels of urinary IL-6 and PI values than patients without renal inflammatory foci, and that there was a significant correlation between urinary IL-6 levels and PI values. These studies suggest the presence of renal parenchymal inflammatory lesions during the acute phase of KD, which can result in sterile pyuria.

In addition, we recently reported a case of acute cystitis in a patient with KD. This case suggested that sterile pyuria in KD may originate from the bladder due to cystitis[33].

KD ASSOCIATED WITH URINARY TRACT INFECTION

Pyuria is not always sterile in KD. Ooto *et al*[34] first reported a KD patient with urinary tract infection (UTI) due to Klebsiella oxytoca and left vesicoureteral reflux (VUR). Shiono *et al*[35] reported a KD patient with acute pyelonephritis due to *Escherihia coli* (*E. coli*) and left VUR. Horikawa *et al*[36] and Husain *et al*[37] individually reported KD patients with UTIs caused by *E. coli* and without any urinary tract abnormalities.

Benseler *et al*[38] reviewed the clinical, laboratory and microbiological data of 129 patients with KD and reported that 33% of patients with KD had concurrent infections at the time of KD diagnosis, 4 patients with KD developed UTIs due to *E. coli* (3 patients) or Klebsiella (1 patient), and concurrent infections at the time of diagnosis of KD did not affect the patient response to treatment with intravenous immunoglobulin. Wu *et al*[39] retrospectively reviewed the clinical and laboratory data of 75 patients with KD who underwent urinalysis and urine bacterial cultures, and reported that 34 (45.3%) patients had sterile pyuria, 8 (10.7%) had bacterial pyuria and 2 (2.7%) had UTIs without pyuria, 6 of 10 (60%) patients with UTIs were ⩽ 12 mo of age, and there were no significant differences in clinical presentations, laboratory data, and response to treatment between those with and without UTI.

Taken together, pyuria is not always sterile. The clinical phenotypes do not differ between those with or without UTIs. Because some KD patients with UTIs have urinary tract abnormalities such as VUR, a complete UTI workup including renal ultrasound, voiding cystourethrogram and/or dimercaptosuccinic acid renal scan is recommended[39].

CONCLUSION

Pyuria is a common feature of patients with KD, occurring in 30%-80% of patients. KD patients with pyuria are more likely to be ⩽ 1 year of age, exhibit more severe inflammatory reactions, and may have sub-clinical renal injuries. Sterile pyuria in KD patients originates from the urethra, the kidney as a result of mild and sub-clinical renal injuries, and/or the bladder due to cystitis. Pyuria is not always sterile in KD and results from UTI. Because some KD patients with UTIs have urinary tract abnormalities, a complete UTI workup is recommended.

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CASE REPORT

Endobronchial tumor in children: Unusual finding in recurrent pneumonia, report of three cases

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Abstract

We are reporting 3 cases of pediatric endobronchial tumors presented with recurrent pneumonia. The median age of patients, at time of presentation, was 10.6 years. All patients presented with recurrent pneumonia with a mean time to occurrence, after onset of symptoms, of 14 mo. Bronchoscopy was early performed as part of diagnostic work-up and it revealed an endobronchial mass in every case. Complete surgical resection was performed in all cases, with lung preservation in two of them. Neither post-operative chemotherapy nor radiotherapy was required. The mean duration of follow-up was 7 years and all patients are still alive and disease-free. Recurrent pneumonia, in pediatrics, should raise the suspicion of an obstructing lesion, congenital malformation or systemic disease. A systematic approach is useful for organize the clinicians initial workup. Prompt diagnosis allows parenchymal-sparing surgery, which offers the best chance of cure and reduces clinical and functional complications in these patients.

Key words: Recurrent pneumonia; Pediatric; Endobronchial tumor; Mucoepidermoid tumor; Carcinoid tumor

Core tip: The role of a systematic diagnostic work up in determining the risk of rare conditions in pediatric recurrent pneumonia has been delineated. This case series not only present 3 cases of rare pediatric endobronchial tumors, but also applies early bronchoscopy as a tool to rule out the presence of tumors of the respiratory tree in case of recurrent pneumonia. Prompt diagnosis allows parenchymal-preserving surgery, which offer the best chance of cure and reduce clinical and functional complications in these patients.

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INTRODUCTION

Bronchial adenomas account for 5% of all primary pulmonary neoplasms in children and include both carcinoid and mucoepidermoid tumors[1-4]. These are considered as low-grade and slow growing malignant neoplasm and their evolutions are usually favorable after surgery[1,5,6]. Pathologic findings of endobronchial tumors can represent a wide array of symptoms as atelectasis or recurrent pneumonia, as the consequence of bronchial obstruction[3,5,7,8]. We describe 3 pediatric cases of endobronchial adenomas, occurring over a 10-year period at our hospital. All patients had history of recurrent pneumonia meaning more than 1 episode of pneumonia in 1 year or more than 3 episodes in a lifetime. We discuss their diagnostic work-up and clinical outcome. We suggest, for patients with recurrent pneumonia, early referral for bronchoscopic evaluation for accurate differential diagnosis. A delay in diagnosis of endobronchial tumor may lead to local and distant spread and permanent lung damage as consequence of radical surgery.

CASES REPORT

Case 1

A 14-year-old boy presented with a history of recurrent bronchopneumonia, 5 episodes in the last 18 mo, unresponsive to antibiotic therapy. On clinical examination, he showed no breathing sounds on left hemithorax with thump bluntness. A chest X-ray showed a collapsed left lung with tracheal deviation (Figure 1A). A computer tomography (CT) scan showed a left endobronchial mass arising from the main bronchus with omolateral collapse of the lung and consensual pleural effusion (Figure 1B). Bronchoscopy revealed a polypoid, obstructive mass in the left main bronchus. The biopsy yielded positive result for typical endobronchial carcinoid. At surgery, a wide and infiltrating polypoid mass on main left bronchus was found so left pneumonectomy was performed (Figure 1C). The final histologic examination showed a 1.5-cm polypoid mass that was made up of monomorphic cellular proliferation with a low mitotic proliferative rate. Immunohistochemistry was strongly positive for chromogranin and weak for synaptophysin (Figure 1D). The adjacent pulmonary parenchyma was suggestive of consensual pneumonia. Octeotride scintigraphy showed a physiological tracer without metastasis. At 10 years follow up the patient had neither clinical nor radiological evidence of recurrence of the tumor.

Case 2

A 10-year-old girl was admitted for evaluation and treatment of 1-year history of left pneumonia with 3 consecutive episodes. On examination she was afebrile, dullness to percussion and decreased breath sounds over the left upper lobe of the left lung. A chest X-ray showed a left pulmonary collapse with pleural effusion and an image suspected of left bronchial obstruction. CT scan demonstrated solid and lobulated mass with calcification and atelectasis in the posterior segment of the left upper lobe. Bronchoscopy revealed a polypoid tumor in the left main bronchus. Biopsy resulted in low-grade mucoepidermoid carcinoma. A left superior sleeve lobectomy, with end-to-end anastomosis between the main and inferior lobar bronchus, was performed. The post-operative course was uneventful. Follow up at 7 years was good and spirometric assessments showed forced expiratory volume in 1 s and forced vital capacity within normal range.

Case 3

An 8-year-old boy presented with a 1-year history of bronchospasm and recurrent pneumonia, 4 episodes, unresponsive to corticosteroids, bronchodilators and antibiotic therapy. He was afebrile and his chest examination was unremarkable. Chest X-ray and CT revealed left bronchiectasis and left upper lobe consolidation as for pneumonia. Bronchoscopy revealed a polypoid mass arising from the left main bronchus. Histologic examination showed low-grade mucoepidermoid carcinoma (Figure 2). A left bronchial resection, with end-to-end anastomosis of the left main bronchus, was performed. Post-operative course was uneventful. The patient has remained disease-free at 5-year clinical and radiological follow-up.

DISCUSSION

Recurrent pneumonia is defined as more than 1 episode of pneumonia in 1 year or more than 3 episodes in a lifetime, with radiographically documented clearing episodes[4,7,9]. The number of host defects that can predispose to recurrent pneumonia is high, and differential diagnosis is often challenging. The first step is to confirm the diagnosis of recurrent pneumonia; it should be made by chest X-ray (2 projections) that reveals pulmonary consolidation on more than one occasion[7]. The presence of a persistent infiltrate in the same area, in the interval between pneumonias, could represent treatment failure or localized obstruction[7]. In these cases both CT scan and fiber optic bronchoscopy should be performed to make differential diagnosis between congenital lung defects (congenital adenomatoid cystic malformation, pulmonary sequestration, congenital emphysema), external compression of conducting airways, intraluminal foreign bodies or endobronchial masses[3,4,7,9,10]. Primary endobronchial tumors are rarely considered as predisposing factors for recurrent atelectasis or respiratory tract infection[2,3]. The symptoms are related to airway obstruction and

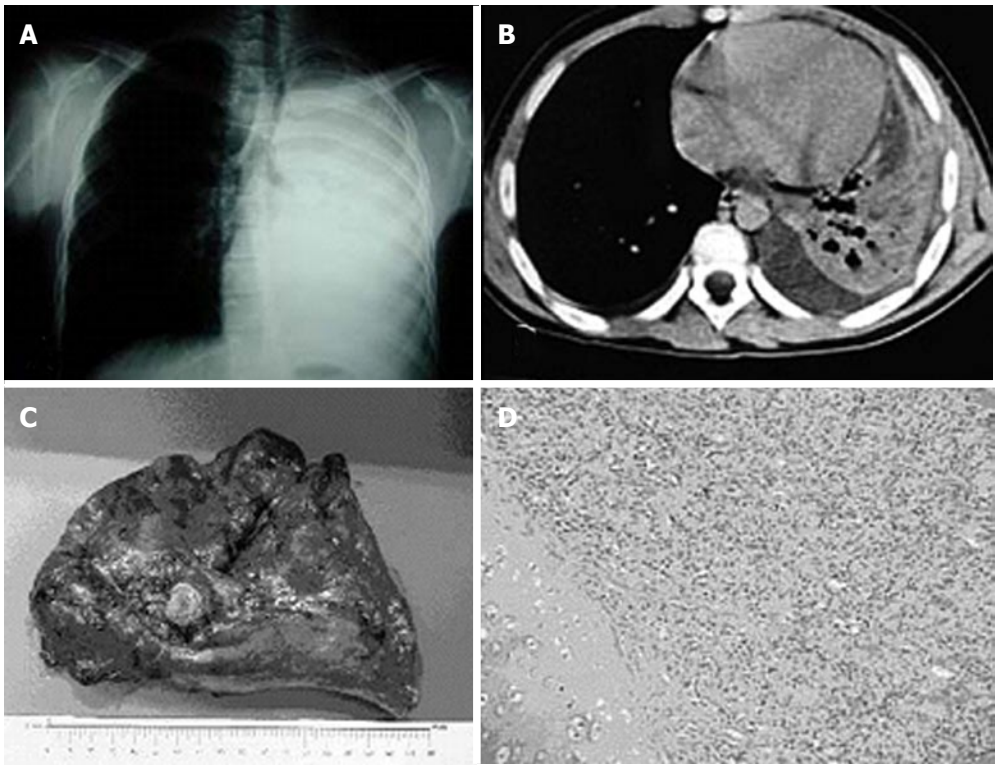

Figure 1 Case 1, endobronchial carcinoid. A: Antero-posterior chest X-ray diagnosed at the onset of the last episode of pneumonia, demonstrating a complete collapse of the left lung with hyperdistension of controlateral one. There is also an aerial bronchogram with a block before the carena; B: Axial computed tomography-scan (CT-scan), performed before operation, demonstrating atelectasis of left lung with pleural effusion; in particular we can observe the obstruction of the left main bronchus; C: Gross findings of the resected left lung, on lateral surface a 1.5 cm polypoid mass obstructing the left main bronchus, firmly adherent to the wall and with a differing consistency from hard to elastic; D: The tumor was pathologically diagnosed as endobronchial carcinoid: on the left the cartilaginous wall and on the right the tumor (HE stain x 20). Monomorphic proliferation with cells forming pseudoacinouses patterns. Absence of atypical cells or abundant mitosis.

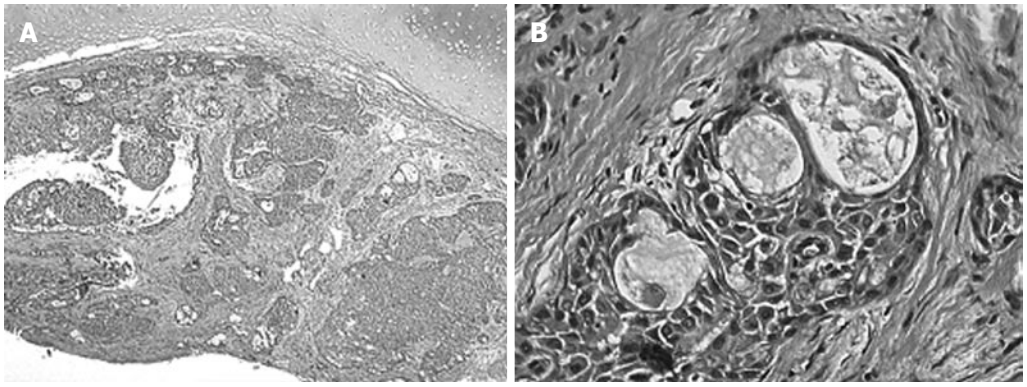

Figure 2 Case 3, mucoepidermoid carcinoma, histological findings. A: The tumor was pathologically diagnosed as mucoepidermoid Carcinoma (HE stain x 5). Neoplastic infiltration of the bronchial submucosa characterized by a mixture of glands, tubules, cysts and solid areas; B: Glandular component of the tumor, lined by columnar mucinous cells and containing mucin, is intimately admixed with solid islands composed of squamous and intermediate cells (HE stain x 63).

include: recurrent pneumonia, persistent cough, sometimes associated with hemoptysis, wheezing and chest pain[1,11]. The lack of specificity of these symptoms may account for a median diagnostic delay of 5.85 ± 5 mo[5]. We describe 3 cases of recurrent pneumonia with mean time to presentation after onset of symptoms of 14 mo. In childhood, the most common primary lung tumors are malignant, with only approximately one-third benign[4]. The rarity of primary lung tumors is emphasized by the findings of an extensive review of the literature, in which the ratio of primary tumors to metastatic tumors to non-neoplastic lesion of the lung is 1:5:60[3,4]. Endobronchial tumors include benign lesions such as hemangiomas, papillomas, inflammatory pseudotumors (plasma cell granulomas), leiomyomas and mucus gland tumors. The malignant ones include: bronchial adenomas (an obvious misnomer), carcinoids, mucoepidermoid carcinomas, and adenoid cystic carcinoma[3,4].

Bronchial carcinoid is the most common primary endobronchial neoplasm; it makes up about 80% of malignant pulmonary neoplasm in children[3,8]. The

tumor arises from the Kulchitsky cell of the respiratory epithelium. Carcinoid tumors can be divided in typical and atypical forms with the latter exhibiting histologically malignant features and aggressive clinical behavior. This histological and clinical distinction is not clear in pediatric population due to the rarity of this pathology[3]. Our case although showed typical histology with benign behavior. In the literature, the median age at diagnosis in children in 10.5 ± 3 years, but we described the case of a patient who came to our attention at 14 years of age[5]. This neoplasm can arise in the lobar bronchi (75%), in the mainstream bronchi (10%), causing atelectasis, or in lung periphery (15%), and the right lung is more often involved then the left one[8,11,12]. These tumors are described as endobronchial polypoid masses with intraluminal, mural and extra bronchial components, which could completely obstruct the bronchus and interfere with distal ventilations giving reason of respiratory symptoms as dyspnea and wheezing or further complications as pneumonia and atelectasis[5,8]. Rarely, patients with tracheobronchial carcinoid tumors present with carcinoid syndrome, such as: Cushing's syndrome, acromegaly, or the inappropriate antidiuretic hormone secretion[12]. Distant metastasis or local recurrences are rarely reported, especially in cases with atypical histology. As in our cases, the chest X-ray may show findings of partial or total bronchial obstruction as atelectasis, although it is reported as normal in about 10% of patients[8,11]. CT scan is the most sensitive noninvasive imaging method for bronchial abnormalities. It allows the best resolutions of a pulmonary mass, defining: the relationship with the tracheobronchial tree, the presence of calcification, reported in 4%-26% of the cases, concomitant lymphadenopathies, and the grade of contrast enhancement[8,11]. However, bronchoscopy is considered as the gold standard for diagnosis and, despite the risk of hemorrhage, endobronchial biopsy has been shown to give the highest yield of positive diagnosis[5]. Sleeve or bronchoplastic resections are preferred to more extensive resection of centrally located carcinoids, even if atypical carcinoid requires a more extensive resection with lymph node dissection[3,8,13]. Our patient underwent pneumonectomy due to the extensive infiltration of the lesion as consequence of late in diagnosis. Techniques for bronchoscopic resection include eletrocautery, NdYAG laser and piecemeal removal with biopsy forceps, but they are considered inadequate and may lead to tumor recurrence[14]. The recurrence rate is estimated at 8.2%, with overall survival of 92% at 10 years[13]. Systematic monitoring after the surgical intervention is recommended with clinical examination and chest X-ray. We followed up our patients for 10 years without evidence of recurrence. Early bronchoscopy should be performed if clinical symptoms, as recurrent pneumonia, and radiological findings are suggestive of tumor recurrence.

Bronchial mucoepidermoid carcinoma is a slow-growing, malignant glandular epithelial neoplasm that origins from excretory duct reserve cells of serous and mucous glands. It, particularly, involve the respiratory mucosa[1,15]. These tumors are rare in children, accounting for 2.5% to 7.3% of endobronchial adenomas and representing 0.1% to 0.2% of primary lung cancers[1,3,16]. Although the age range of patients is extensive, cases involving patients < 10 years old are rarely observed[2]. Our patients had respectively 10 and 8 years of age. The clinical symptoms are mainly related to airway obstruction and include pneumonia or recurrent pneumonias up to 48%[2,11]. Both our patients presented with a clinical history of recurrent pneumonia, respectively 3 and 4 episodes. Common radiological findings, on CT scan, are bronchial nodular mass with or without post-obstructive pneumonia, atelectasis, or a solitary nodule and lymphadenopathies should be always checked[8,15]. Treatment consists of a careful surgical removal of the tumor, the lymphnodes and vascular and perineural infiltration should be evaluated. When technically feasible, a sleeve resection of the involved bronchus is recommended[5]. The prognosis is good in up of 95% of the cases and low and intermediate grade carcinomas, with complete resection, do not require chemotherapy or radiotherapy[1,12]. In the present study lobectomy was performed in one-case and sleeve resections in other one; thus allowed a considerable portion of the lung parenchyma to be preserved. The risk of recurrence justifies a long-term clinical follow-up, indeed bronchoscopy should be performed only in case of severe respiratory symptoms[5]. Our patients had no clinical or radiological evidence of disease recurrence during a 10 and 5 years follow-up period.

Endobronchial tumors are rare in the pediatric population; these tumors most often present with symptoms of recurrent pneumonia or wheezing. In case of respiratory symptoms that do not improve with standard treatment (antibiotics, bronchodilators), further work up with CT scan and bronchoscopy is advisable to rule out the presence of an obstructive process as endobronchial tumors. Early diagnosis may help in determining optimal treatment plan that can increase the possibility of implementing a selective procedure, avoiding the pulmonary functional impairment and chest wall deformity that can result from extensive lung resection and improve outcome.

COMMENTS

Case characteristics

A series of 3 pediatric patients with a median age at presentation of 10.6 years, all presented with recurrent pneumonia, non-responsive to medical standard therapy.

Clinical diagnosis

Case 1: No breathing sounds with thump bluntness and dullness to percussion on left hemithorax; Case 2: Dullness to percussion and decreased breath sounds over the left upper lobe of the left lung; Case 3: No pathological findings on thoracic objective examination.

Differential diagnosis

Cystic congenital adenomatoid malformation, congenital emphysema, lung mass, lung abscess, pneumonia.

Laboratory diagnosis

Blood count cell and metabolic panel tests shows, only, elevated white cells blood count.

Imaging diagnosis

Case 1: An endobronchial mass arising from the left main bronchus with omolateral collapse of the lung and consensual pleural effusion; Case 2: A solid and lobulated mass with internal calcification and atelectasis in the posterior segment of the left upper lobe; Case 3: Left bronchiectasis and left upper lobe consolidation.

Pathological diagnosis

Case 1: Bronchoscopy and biopsy revealed typical endobronchial carcinoid; Case 2: Bronchoscopy and biopsy revealed low-grade mucoepidermoid carcinoma; Case 3: Bronchoscopy and biopsy revealed low-grade mucoepidermoid carcinoma.

Treatment

Case 1: The patient was treated with a left pneumonectomy; Case 2: The patient was treated with a left superior sleeve lobectomy, with end-to-end anastomosis between the main and inferior lobar bronchus; Case 3: The patient was treated with a left bronchial resection, with end-to-end anastomosis of the left main bronchus.

Related reports

Endobronchial tumors are rare in childhood and are not often considered in the differential diagnosis of recurrent pneumonia and bronchoscopy is not usually considered as first diagnostic approach.

Term explanation

Bronchial carcinoid is a tumor that arises from the Kulchitsky cell of the respiratory epithelium. It is divided in typical and atypical forms. Bronchial mucoepidermoid carcinoma is a slow-growing, malignant glandular epithelial neoplasm that origins from excretory duct reserve cells of serous and mucous glands, in particular that find within the submucosal of the respiratory mucosa

Experiences and lessons

This case series not only represents 3 rare cases of pediatric endobronchial tumors, but also underline the need of systematic diagnostic work-up, which should consider bronchoscopy, to prevent delayed diagnosis of potential malignant lesions.

Peer-review

The authors have described three rare cases of pediatric endobronchial tumors that presented with recurrent pneumonia. The article highlights the need of systematic approach to recurrent pneumonia by clinicians to prevent complications due to rare conditions. Prompt diagnosis allows parenchymal-preserving surgery, which offer the best chance of cure and reduce clinical and functional complications in these patients.

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