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Defining atypical croup: A case report and review of the literature

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1. Introduction

Croup develops in more than 80,000 Canadian children annually and accounts for 5% of emergency hospital admissions in children under 6 years of age [1]. In its current use, a diagnosis of group encompasses a number of respiratory illnesses characterized by varying degrees of inspiratory stridor, cough, and hoarseness resulting from inflammation and narrowing of the larynx. Viral group (acute laryngotracheitis) refers to the typical croup syndrome that occurs in children as well as parainfluenzal virus, and respiratory syncytial virus (RSV) [3,4]. This results in erythema and swelling of the lateral walls of the trachea and larynx, leading to epithelial necrosis and laryngeal and subglottic narrowing secondary to inflammation [3,5]. The disease process is self-limited with resolution typically within one week [6,7]. In mild cases, a single dose of oral dexamethasone may be administered. In moderate to severe cases, dexamethasone and nebulized epinephrine are the mainstay of therapy. In cases of failure of medical treatment, progression to exhaustion from increased work of breathing, hypercapnic or hypoxic respiratory failure, or imminent airway obstruction, treatment with endotracheal intubation is warranted. The incidence of intubation is approximately 3% for all patients admitted for group [8-10].

In the medical literature, there have been attempts to sub-classify and define group based on infectious etiology, clinical recurrence or severity. Patients with uncharacteristic presentations or abnormal natural history are commonly diagnosed with atypical group. The use of this term leads to several difficulties in the management of these
patients in the acute care setting. Given there is no definitive diagnostic or management pathway for atypical croup, patients are often subject to radiographic studies and operative assessments that require a general anesthetic. The primary objective of this case report and systematic review is to evaluate the published definitions of atypical croup. The secondary objectives are to summarize its diagnosis, etiologies, and management, and identify the patient characteristics that may result in intubation or tracheostomy and propose a management pathway.

2. Case report

2.1. Initial presentation

A previously healthy 3-year-old male manifested a low-grade fever, progressive stridor, a barking cough, tracheal tugging and suprasternal in-drawing 7 days following an upper respiratory tract infection. Despite a 3-day course of amoxicillin and prednisone, his work of breathing and stridor increased, requiring nebulized epinephrine administered at a regional emergency department. He was subsequently transferred to the Alberta Children’s Hospital (ACH) pediatric intensive care unit (PICU) due to airway concerns. Although he remained non-toxic and playful, his biphasic stridor only improved briefly with medical therapy. As a result, a lateral neck x-ray and computed tomography (CT) of the neck were performed on day 2 of admission to rule out a subglottic lesion.

2.2. Clinical diagnosis

CT imaging demonstrated diffuse edema and narrowing of the glottis, subglottis, and upper trachea in keeping with croup. Operative laryngoscopy and bronchoscopy performed 2 days after admission revealed an inflamed subglottis approximately 4–5 mm in diameter (Cotton Myers System Grade III). No other abnormalities were found. Despite repeated nebulized epinephrine and intravenous dexamethasone administrations, the patient’s stridor remained biphasic with little to no improvement. On post-admission day 7, the patient’s respiratory status deteriorated such that he required endotracheal intubation. This was performed in the OR allowing for repeat laryngoscopy and rigid bronchoscopy, which revealed a narrower subglottic airway than was seen during previous bronchoscopy (still Cotton Myers Grade III). Due to the degree of narrowing, a 3.0 endotracheal tube was placed. A mucosal biopsy performed intraoperatively showed respiratory epithelium with prominent lymphoid aggregates and abundant reticular fibres in the subepithelial stroma. These lymphocytes were diffusely positive for CD21 and B-cell markers, CD45, and CD3. There was no significant cytological atypia. Tracheal swabs were negative for bacteria, fungus, and EBV. Nasopharyngeal swabs were positive for rhinovirus RNA only. IgM testing for mycoplasma pneumoniae was negative.

Because the patient’s subglottic narrowing was felt to be firm intraoperatively, magnetic resonance (MR) imaging of his neck was ordered post-operatively. This showed a narrow 3 mm subglottis without T2 hyperintensity. A 7 mm × 5 mm round, well-circumscribed focus of non-enhancement posterior to the upper trachea was appreciated also, suggestive of a proteinaceous cyst. This lesion was not seen on later endoscopies and may have been an artefact of biopsy. No additional abnormalities were seen.

Due to the unusual nature of this presentation, rheumatologic work up was performed. This showed normal serum anti-nuclear antibody, glomerular basement membrane antibody, anti-neutrophil cytoplasmic antibody, anti-MPO and proteinase 3 antibody (PR3), c-reactive protein, ferritin, lactate dehydrogenase, and quantitative rheumatoid factor levels. Similarly, immunologic investigations showed normal immunoglobulin E and IgE aspergillus antibody levels.

2.3. Management

Despite 4 days of scheduled systemic steroids in the PICU, an endotracheal cuff leak was not achieved; therefore a tracheostomy was performed in anticipation of prolonged intubation 14 days after presentation to the emergency department and 21 days after the start of his symptoms.

Six days following operative tracheostomy, a repeat operative bronchoscopy showed a 5 mm midline lesion on the posterior tracheal wall that was 3 cm distal to his glottis, superior to the distal tip of the tracheostomy tube. Excisional biopsy showed chronic lymphocytic inflammation, fibrin exudate, and early granulation consistent with an inflammatory pseudotumour. Following one month of watchful waiting, suspension laryngoscopy and rigid bronchoscopy demonstrated significant improvement in subglottic patency. However, a tracheostomy was maintained due to continued narrowing of his airway. On follow-up bronchoscopy, a suprastomal granuloma was seen and obliterated with a YAG laser. Repeat rigid bronchoscopy performed 3 months later showed resolution of the posterior tracheal wall mass and subglottic stenosis. He was decannulated intraoperatively and admitted to the PICU for overnight observation. He was discharged the following day with no further concerns, 219 days after his initial presentation. These findings most likely resulted from gross inflammation secondary to RSV given the absence of any other anatomical abnormality on radiographic and operative assessment.

3. Systematic review

We aimed to identify all full-text, peer-reviewed publications pertaining to atypical croup. The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) reporting guideline was adapted for the current review. Published studies pertaining to atypical croup were found utilizing the Ovid MEDLINE® and EMBASE databases from inception to January 1st, 2019 (Fig. 1). All peer-reviewed studies in children less than 18 years of age and studies in the English language were included. The following search terms were used: croup, laryngitis, laryngotracheitis, and laryngotracheobronchitis. Results were combined with the term atypical to retrieve the articles. Articles were screened by two authors and the reference lists of chosen articles were searched to further identify relevant articles. Articles with a focus on atypical presentations of croup were included. Reviews, commentaries, and editorials were excluded. The information extracted consisted of author, year, level of evidence, study design, demographics of the patient sample, including age and symptom duration, diagnostic data, etiology, and medical treatment.

4. Results

Two authors examined 41 articles and identified 12 that met the inclusion criteria (Table 1). The search strategy and flow diagram are presented using the PRISMA guidelines. Results focused on identifying definitions of atypical croup in the literature. The etiology, incidence, prevalence, diagnosis and management of atypical croup were secondary objectives.

4.1. Definitions of atypical croup

Definitions of atypical croup varied in the examined studies. Several articles included a recurrent course within the definition. For instance, Cooper et al. (2012) defined croup as atypical if a child had more than 4 recurrent episodes, however Waki et al. (1995) suggested 2 or more episodes necessitating inpatient care [11,12]. Several studies also noted an atypical age of presentation as part of their definition. Chauhan et al. (2007) defined an age of presentation less than 6 months as atypical while Cooper et al. (2012) added an upper limit of greater than 3 years of age [11,13].
Several authors included the severity of presentation and unresponsiveness to medical therapy as defining features. Farmer and Wohl (2001) defined severity based on the need for any inpatient admission while Hatherill et al. (2001) defined severity based on the need for PICU admission due to severe subglottic stenosis [14,15]. Furthermore, prolonged duration of symptoms was a common criterion listed in definitions of croup in the literature search. Inglis Jr. (1993) and O’Niel et al. (2013) defined croup as atypical if symptoms lasted longer than seven days, although other studies did not provide a specific duration [16,17]. Finally, croup associated with an uncommon pathogen was also defined as atypical. In a study by Low et al. (2012), fungus was identified as the causative organism while Miller et al. (1982) reported Chlamydia trachomatis [17–19].

### 4.2. Etiology and incidence of atypical croup

The etiology of atypical croup included several organisms not normally associated with croup. Several studies noted herpes simplex virus type 1 as the causative organism, associated with oral and laryngeal ulcers. Low et al. (2012) reported the fungus *Curvularia* in a single case presenting as an atypical croup-like syndrome in an immunosuppressed child while Miller et al. (1982) reported *Chlamydia trachomatis* and *Staphylococcus aureus* in atypical croup [18,19]. Hatherill et al. (2001) reported other bacterial species; however it was unclear if these pathogens were associated with cases of atypical croup in their chart review [15]. The incidence of atypical croup was not reported in any of the studies reviewed.

### 4.3. Diagnosis of atypical croup

Croup is primarily a clinical diagnosis, however the cases of atypical croup reviewed often required further investigation. In our review, endoscopy was used to aid diagnosis in all 12 studies. Findings on endoscopy varied based on etiology. Ulcerations were reported in cases of herpetic croup by O’Niel et al. (2013), Inglis Jr (1993), Chauhan et al. (2007), and Krause et al. (1998) [13], [16], [17], [20]. In a retrospective chart review, Hatherill et al. (2001) assessed the presence of ulcerative lesions on microinoscopy in children with croup who were admitted to the PICU [15]. Laryngeal ulcerations were identified in 10% of children admitted while 18% had gingivostomatitis consistent with HSV infection. Furthermore, in a review performed by Cooper et al. (2012) of 80 children diagnosed with atypical croup, 33 had large airway lesions, which included subglottic stenosis, laryngeal clefts, subglottic hemangiomas, tracheomalacia, and laryngomalacia [11]. In addition, the authors reported associations between atypical croup and atopic conditions such as eosinophilic esophagitis. The authors recommended that endoscopy be coupled with allergy and gastrointestinal investigations in children with atypical croup. Barnes et al. (1999) described a case where laryngoscopy revealed two large subglottic cysts in addition to subglottic stenosis [21]. Finally, Waki et al. (1995) noted an association between gastroesophageal reflex disease (GERD) and recurrent croup [12]. Patients with GERD had shorter time periods between episodes of croup and younger age of presentation. Findings associated with GERD, including edema and erythema of the arytenoid and tracheal mucosa, were identified in 47% of children assessed for recurrent croup and 25% showed anatomical airway narrowing with direct laryngoscopy and bronchoscopy.

### 4.4. Management of atypical croup

The cornerstone of croup management is nebulized epinephrine and systemic corticosteroid. In cases of atypical croup, management often differs. Chauhan et al. (2007) discussed treatment with corticosteroids in the setting of HSV-induced atypical laryngitis and suggested that corticosteroid use may delay diagnosis and initiation of appropriate management.

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**Fig. 1.** The search strategy and flow diagram as per PRISMA guidelines.
| Article | Study Type | Demographics | Microbiology | Investigations | Treatment | Definition of Atypical Croup |
|---------|------------|--------------|--------------|---------------|-----------|-----------------------------|
| Chauhan et al. (2007) | Case Series | n = 2 Mean age 15 months Unknown symptom duration | Herpes simplex virus 1 (n = 2) | Laryngoscopy | Systemic dexamethasone Nebulized epinephrine IV acyclovir Intubation | Presentation < 6 months of age, or beyond toddler stage OR Unresponsive to supportive measures OR Recurrence or progression to fulminant course |
| Cooper et al. (2012) | Case series with chart review | n = 80 Mean age 48 years Unknown symptom duration | Unknown | 80 children underwent laryngoscopy | Unknown | Croup episodes in a child 6 months old or younger, older than 3 years, or with recurrent episodes of croup (4 or more episodes in total) |
| Hatherill et al. (2001) | Retrospective chart review | n = 263 Mean age unknown (median age 14 months) Unknown symptom duration | Herpes simplex virus (n = 3) Cytomegalovirus (n = 1) Haemophilus influenzae (n = 5) Staphylococcus aureus (n = 2) Streptococcus pneumoniae (n = 1) Providencia retgeri (n = 1) mixed commensals | 147 children underwent microlaryngoscopy copy | 15 children received IV acyclovir 9 children underwent nasotracheal intubation 5 children required tracheostomy | Increased severity or duration |
| Inglis Jr. (1993) | Case series | n = 2 Mean age 16 months Mean symptom duration 24 days | Herpes simplex virus 1 (n = 2) | Laryngoscopy | Prednisolone Acyclovir sodium Epinephrine Amoxicillin/clavulanate potassium Nafcillin sodium Dexamethasone sodium phosphate Intubation (n = 1) | Prolonged course (> 7 days) |
| Harris et al. (1987) | Case series | n = 1 Mean age 18 months Symptom Unknown symptom duration | Herpes simplex virus (n = 1) | Rigid bronchoscopy | Ampicillin Methylprednisolone Epinephrine Oral dexamethasone | Prolonged course |
| O’Niel et al. (2013) | Case series | n = 2 Mean age 15 months Mean symptom duration 28 days | Herpes simplex virus 1 (n = 1) | Direct laryngoscopy with rigid bronchoscopy | Heliox Nebulized epinephrine Methylprednisolone IV acyclovir IV amphotericin B Oral voriconazole IV caspofungin | Atypical if lasting more than 7 days or does not respond to appropriate treatment |
| Low et al. (2012) | Case report | n = 1 Mean age 8 years old Unknown symptom duration | Curvularia species (n = 1) | Laryngoscopy Bronchoscopy | IV amphotericin B Oral voriconazole IV caspofungin | Group cause by an atypical pathogen |
| Krause et al. (1997) | Case report | n = 2 Mean age 12 months Mean symptom duration 3.5 weeks | Herpes simplex virus 1 (n = 2) | Fibre optic laryngotracheobronchoscopy | IV ceftazidime IV dexamethasone Nebulized epinephrine Oral betamethasone | Prolonged course |
| Miller et al. (1982) | Case report | n = 1 Mean Age 3.5 years | Chlamydia trachomatis Staphylococcus aureus | Rigid bronchoscopy | IV Nafcillin Erythromycin Intubation | *Describes bacterial tracheitis as an atypical croup like syndrome, consisting of a more severe and prolonged presentation, affecting older children, often requiring an artificial airway, and purulent subglottic exudate associated with culture of Staphylococcus aureus from tracheal secretions |

(continued on next page)
therapy, resulting in prolongation of the clinical course [13]. Steroid administration was also discouraged with additional causes of atypical laryngitis including inflammatory processes, such as GERD and alternate viral processes, such as recurrent respiratory papillomatosis. Inglis Jr. (1993) proposed that prolonged use of corticosteroids resulted in susceptibility to herpetic croup and suggested that corticosteroid use be limited to 48 h [16]. Acyclovir was given following cessation of corticosteroid medication in their case report.

Atypical croup often necessitated definitive airway management in the studies reviewed. Hatherill et al. (2001) reported that 9 out of 148 children (6%) admitted to the PICU for croup needed intubation with a median duration of 4 days [15]. Five children required tracheostomy to prevent mucosal damage secondary to the mechanical trauma. The clinical decision to proceed to tracheostomy was based on severe subglottic ulceration and narrowing such that a size 3.0 endotracheal tube could not be passed. Intubation was deemed necessary due to subglottic edema in HSV laryngitis reported by Chauhan et al. (2007), Inglis Jr. (1993), and O’Neil et al. (2013) [13], [16], [17]. Barnes et al. (1999) reported a case in which marsupialization of subglottic cysts lead to resolution of symptoms [21].

5. Discussion

Presented is a case of croup in a child that occurred secondary to RSV infection. His symptoms were relapsing and remitting in nature, with only short-lived responses to conventional treatments, requiring PICU management, intubation, and tracheostomy. A pseudotumor identified on bronchoscopy suggested an inflammatory etiology, however rheumatologic and immunologic workup were negative. Complete recovery was unusually prolonged necessitating continued maintenance of his tracheostomy and repeated operative bronchoscopy for airway assessment.

This case report of croup is atypical in three notable ways: (1) the prolonged presentation and unresponsiveness to medical therapy (2) the need for a surgical airway despite 21 days of maximal medical therapy; and (3) identification of an inflammatory airway lesion suggesting a potential underlying primary inflammatory disease process. This case offers insight into the diagnostic challenges of atypical croup and highlights the role of surgical airway management in cases unresponsive to medical therapy.

Typical croup syndromes are usually self-limited in nature and responsive to medical therapy [6]. In unusual cases of croup presentations, a different approach to diagnosis and management may be necessary. However, there is no commonly accepted definition of atypical croup. Thus, we performed a systematic review on atypical croup to identify definitions available in the literature. Furthermore, we sought to identify diagnostic approaches used to investigate these atypical presentations and reported management strategies.

Our review identified 12 English language articles on atypical croup in the pediatric population. In our search the term atypical croup was used in the literature in a variety of contexts. Recurrent episodes, croup in a child who lies outside the age range of typical viral croup, prolonged or severe episodes, or croup occurring due to uncommon etiology were all observed.

Typical viral croup is most commonly associated with the parainfluenza viruses, but is also associated with adenovirus, RSV, rhinovirus and the influenza viruses [4]. Our search revealed several infectious etiologies associated with atypical croup, the most common of which was HSV. This association may be linked to immunosuppressive effects of corticosteroid administration due to treatment of an initial typical croup presentation [13,15,16,20]. In one immunosuppressed child, the fungus Curvularia was isolated [18]. This suggests that immune modulation plays a role in determining croup presentation and severity. Bacterial causes such as Staphylococcus and Chlamydiae species were also reported although distinctions made between bacterial tracheitis and atypical croup were unclear in those studies [15,19].
Moreover, the clinical presentations reported varied in duration and severity. Prolonged duration was a defining factor in assigning the definition of atypical croup in several reports reviewed. Two studies outlined a time period of presentation beyond 7 days as atypical [16,17]. However, several studies noted prolonged duration as a factor without specifying a specific period of time [15,20–22]. Severity was defined very broadly or not at all in most studies, with the most common definition being PICU admission. In studies where mean or median ages were reported, age of presentation was often older than 3 years of age, with the oldest being 11 years of age, or younger than 6 months of age. No cases were reported beyond that lower boundary.

In the literature, the peak incidence of typical croup is cited between the ages of 6 months to 3 years, however presentations of croup up to 6 years of age were not uncommon. The incidence of croup by age reported by Denny et al. (1983) for example was greater than 1 in every 100 children every year until 6 years of age [23]. Based on the incidence found in typical croup literature, the upper bound of 3 years of age proposed for atypical croup appears too low.

Overall, our search suggests that atypical croup is not a unique clinical entity. Rather, it is a term most often used as catch-all diagnosis for presentations that lie outside the common definition of croup. Some studies have proposed more strict definitions of atypical croup, mostly based on recurrent presentations with consideration of age at presentation; however, there remains a gap in knowledge on the incidence of these atypical episodes [11]. This discordance suggests that it may be beneficial to present a broader definition of atypical croup. We therefore propose that atypical croup may be defined as a child who presents with croup that is either: a) severe, necessitating definitive airway management, b) prolonged, symptoms persisting for 7 or more days despite medical therapy, c) untimely, presenting at an age younger than 6 months or older than 6 years, d) associated with an atypical pathogen, or e) presenting with an airway lesion other than the classically described steeple sign on x-ray imaging. Several of these features were present in this case study, in particular symptoms refractory to maximal medical therapy, prolonged duration, a pseudotumour, and airway narrowing persisting for 6 months after initial presentation.

In the case presented, operative endoscopy was utilized to identify a severely narrowed subglottis and inflammatory pseudotumor. Atypical findings on endoscopy were reported in several studies. Large airway lesions such as subglottic clefts, laryngeal ulcers and hemangiomas were found in a variety of cases labelled atypical croup. In one study the prevalence of these lesions was as high as 40% in patients with recurrent croup [11]. The question of who needs endoscopic evaluation was only addressed in one evaluated study by Farmer and Wohl (2001) who proposed endoscopy be undertaken if croup is severe, persists despite treatment, in cases of abnormal imaging or prior to elective surgery [3,14].

Lastly, our patient developed progressive, severe respiratory distress
that required intubation and eventual tracheostomy. We sought to clarify the patient characteristics that place children at risk of intubation or tracheostomy. In one review by O’Niel et al. (2013) of HSV laryngitis, 50% of patients required intubation [17]. The rate of intubation in other forms of atypical croup was not well studied. Furthermore, specific characteristics associated with intubation were not reported. However, Hatherill et al. (2001) described the decision to proceed with tracheostomy based on the prevention of further mucosal damage due to severe ulceration and subglottic narrowing from prolonged intubation [15]. The study noted that 5 children of the 263 reviewed required tracheostomy. In our case the decision to proceed with tracheostomy was based on persistence of airway narrowing following intubation. Overall tracheostomy was only reported in one of the twelve studies reviewed. Thus, other than herpetic croup, there remains a question of the risk factors and patient characteristics that may result in intubation and tracheostomy. Future investigation is warranted to clarify this issue.

The atypical presentation of croup is a common problem faced by emergency physicians, pediatricians and otolaryngologists, and it provides several diagnostic and management challenges. Given the findings from our literature review, we propose a management pathway for atypical cases of croup. We reviewed the Canadian Pediatric Society Position Statement on the “Acute management of croup in the emergency department”, the Seattle Children’s Hospital Croup Pathway, and the “Towards Optimized Practice (TOP) Guidelines on the Diagnosis and Management of Croup” [24–26]. We then adapted our institutional croup pathway, and integrated recommendations from the practice guidelines listed and the conclusions from our literature review on atypical croup to formulate a pathway for atypical croup (Fig. 2).

6. Conclusions

This case offers insights into the diagnostic pathway of atypical croup and highlights the role of surgical airway management in cases unresponsive to medical therapy. Currently, there is no consensus definition for atypical croup. The current literature contains definitions applied to recurrent episodes, yet without agreement on the frequency, duration, or severity. Moreover, atypical croup was used in multiple contexts including airway lesions, bacterial tracheitis, and laryngopharyngeal reflux. Finally, there exists a gap in knowledge of the incidence of atypical croup and factors that result in definitive airway management.

We propose a broad definition of atypical croup and propose a pathway for healthcare providers faced with atypical presentations of croup. At our institution otolaryngology was commonly being consulted for both croup, as well as atypical croup, with ‘atypical’ frequently being applied to cases that, based on our literature review, are, in fact, quite typical. Application of this paradigm within our own centre has not only reduced croup consultations, but provided emergency physicians, hospital pediatricians and intensivists with a common basis from which to approach seemingly unusual or atypical croup presentations.

Declarations of competing interests

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