Isolated pediatric endobronchial primary anaplastic large cell lymphoma

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Abstract
Anaplastic large cell lymphoma (ALCL) is rare, accounting for 10–15% of all childhood non-Hodgkin’s lymphomas. We present a case of primary isolated ALCL in the lung of a 5-year-old boy. An asymptomatic 5-year-old boy had absent breath sounds over his right hemithorax on routine physical exam. Chest X-ray showed complete white-out of the right hemithorax. Chest CT scan demonstrated a mass occluding the right mainstem bronchus. The first bronchoscopic biopsy was reported as an endobronchial neoplasm with an immunophenotype consistent with Ewing’s sarcoma/PNET. One week later, a repeat second bronchoscopy with re-biopsy confirmed the correct diagnosis of ALCL, null phenotype. Clinical and radiological staging revealed no evidence of extrathoracic disease in the past, present, or for three-months after presentation, confirming isolated primary endobronchial ALCL. Complete remission at six-months with polychemotherapy was achieved. Although a rare tumor of the lung, ALCL should be considered in the differential diagnosis of ‘unusual lung neoplasms’ in children.

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Non-Hodgkin’s lymphoma (NHL) of the lung encompasses 3.6% of extranodal lymphomas, and only 0.3% of primary lung neoplasms [1]. These tumors may be classified into two types: a) Type 1: submucosal infiltrates originating from hematogenous or lymphangitic spread in the presence of systemic lymphoma, or b) Type 2: adjacent airway involvement by a localized mass due to direct spread from adjacent lymph nodes [2]. Pediatric non-Hodgkin’s lymphoma most commonly affects the lymph nodes and may be associated with mediastinal involvement and hepatosplenomegaly, with extranodal sites of involvement including the skin, bone, muscle, and lung parenchyma [3].

Anaplastic large cell lymphoma (ALCL), representing 10–15% of pediatric lymphomas, occurs most commonly in children and young adults with a bimodal age distribution [2]. ALCL most commonly affects the sinuses of lymph nodes, and is often associated with involvement of the mediastinum and hepatosplenomegaly. Extranodal ALCL may involve the skin, bone, marrow, soft tissue, pelvis, central nervous system, bone, gastrointestinal tract, lung, pleura, breast, chest wall, retroperitoneum, and spleen [3]. When ALCL involves the lung, it is most commonly the result of advanced disseminated disease. Dissemination is hypothesized to occur via direct invasion from adjacent mediastinal or parenchymal disease, or by lymphatic spread, and/or hematogenous spread. Primary isolated endobronchial ALCL in the pediatric population is exceedingly rare, with very few reports in the published English literature.

We herein report the case of a 5-year-old boy with primary isolated endobronchial ALCL.

1. Case report
A ‘healthy’ asymptomatic 5-year-old boy was discovered, on routine physical examination, to have absent breath sounds over his right hemithorax.

On chest X-ray there was a complete white-out of the right hemithorax with a shift of the mediastinum toward the side of the opacification (Fig. 1A). A chest CT scan revealed the presence of a mass obstructing the right mainstem bronchus with occlusion and surrounding edema (Fig. 1B). Bronchoscopy revealed a soft white fleshy tumor arising from the lumen of the right upper lobe bronchus that was biopsied (Fig. 1C).

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On histopathological evaluation, a tumor composed of sheets of uniform neoplastic “small blue cells” with no characteristic growth pattern was identified (Fig. 2A and B). Tumor cells were strongly positive to CD99 (Fig. 2C) with a Ki67 labeling index estimated at 90%. Tumor cells were negative for S100, CD3, CD20, CD79a, MPO, TDT, PLAP, LMKT, AFP, Synaptophysin, chromogranin, TTF-1, CK7, CD1a, myogenin, pan-keratin, WT-1, and HCG (Fig. 2D). The pathological diagnosis was a neoplasm with an immunophenotype consistent with Ewing’s sarcoma/primitive neuroectodermal tumor (PNET).

A week later the bronchoscopy was repeated to plan for operative resection of the tumor (right upper lobectomy / C6 sleeve resection of the bronchus intermedius) and additional tumor debulking was performed with the tissue being sent for pathological evaluation. Histopathology of this tissue showed uniform polygonal dark blue cells with fine granular chromatin and scant-to-moderate amounts of eosinophilic cytoplasm (Fig. 2E and F). Lesional cells were strongly positive to CD45, with some expression of CD99, which was inconsistent with the previous reported diagnosis of Ewing’s sarcoma. Additionally, the cells were strongly positive to CD30 (Fig. 2G), ALK-1 (Fig. 2H), EMA, TIA-1, and Granzyme. Moderate expression of KP1CD68 was noted, and cells were negative for CD10, CD4, CD8, CD1a, TDT, CD117, and CD34. This immunophenotype favored the diagnosis of anaplastic large cell lymphoma (ALCL). External pathological review of the biopsy material confirmed this suspicion, and the patient was diagnosed with ALCL ALK+ null phenotype. FISH for ALK translocation revealed an abnormal pattern in 54% with evidence of aneuploidy and clonal evolution.

A detailed staging work-up including complete blood count, bone marrow, CSF, plain X-rays ultrasonography, CT, MRI, and skeletal scintigraphy was undertaken. There were no B-symptoms and no extrathoracic involvement was detected. It was therefore determined that this lesion was isolated to the right upper lobe of the lung.

The patient was started on chemotherapy in accordance with the Children’s Oncology Group protocol including intrathecal methotrexate, IV vincristine, IV doxorubicin, and PO prednisone. At
eight months follow-up there was no clinical, pathological, or radiographic evidence of residual disease.

2. Discussion

Endobronchial tumors are rare in children, accounting for only 0.2% of all pediatric malignancies [4]. As such, these are often missed in the differential diagnosis of persistent abnormalities of chest radiographs; therefore, increased awareness is necessary for accurate identification [5]. Benign endobronchial tumors include hamartoma, hemangioma, papilloma, plasma cell granulomas, leiomyomas, and mucus gland tumor; malignant tumors include bronchial adenoma, carcinoids, mucoepidermoid carcinoma, and adenoid cystic carcinoma [4]. Though rare, the most common primary bronchial tumor in childhood is carcinoid tumor, as opposed to adults wherein squamous cell carcinomas predominate [4–6]. The second most frequent tumor of the endobronchium in the first two decades of life is mucoepidermoid carcinoma, the malignant potential of which is controversial [6]. In addition to tumors, other bronchial pathologies must be excluded such as bronchial stenosis, or extrinsic compression due to lymphadenopathy, tuberculosis, or sarcoidosis [7]. Particularly in pediatrics, aspiration of foreign bodies, asthma with mucus plugging, or granulomatous infection should also be considered [5]. Lymphoma rarely presents as an endobronchial lesion. The endobronchial lesion in non-Hodgkin's lymphoma is a rare intrathoracic manifestation and is usually discovered in the background of advanced widely disseminated disease [6]. However, accurate early histological diagnosis is imperative for successful management of such lesions.

ALCL was first recognized in 1982 when the monoclonal antibody Ki-1 was discovered within the Hodgkin's disease cell line. This antibody was subsequently identified as an activation antigen expression on T-cells, B-cells and activated histiocytes, and was assigned to the CD30 cluster. Three years later, in 1985, Stein et al. identified expression of this antigen in large cell lymphomas with prominent sinusoidal invasion. It was then proposed that these CD30 positive tumors represent a distinct clinicopathological entity. In 1988 Kiel classified these neoplasms as "large cell anaplastic lymphoma" in which the term ‘anaplastic’ refers to the abnormal growth of neoplastic cells that do not resemble normal lymphoid cells [8]. Since this initial identification, the genetic and molecular etiology of ALCL has been further elucidated. In the majority of ALCLs (>80–85%), a t(2;5)(p23;q35) chromosomal translocation fuses nucleophosmin (NPM) on chromosome 5 with anaplastic lymphoma kinase (ALK) on chromosome 2 [2]. NPM-ALK plays a role in the aberrant phosphorylation of intracellular substrates resulting in lymphomagenesis. As such, staining for ALK is a specific diagnostic tool and is positive in over 80% of cases [8]. However, ALK dysregulation is not unique to ALCL. ALK alterations have also been reported in many other tumors including inflammatory myofibroblastic tumors, which can also present as an incidental/obstructive endobronchial mass and, though rare, remains a clinically important and pathologically distinct lesion of the respiratory tract in children [9].

ALCL in children is most common at the age of 10–11 years, and is six times more common in males [8]. The most common presentation is with lymphadenopathy; however, precise clinical signs and symptoms depend on the anatomical location of the involved lymph nodes. Fever, bony lesions, spleen/skin infiltration,

<table>
<thead>
<tr>
<th>Ref</th>
<th>Author (Year)</th>
<th>Age</th>
<th>Sex</th>
<th>Presentation</th>
<th>Initial diagnosis</th>
<th>Investigations</th>
<th>ALK status</th>
<th>Cell type</th>
<th>Additional sites of involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kanthan</td>
<td>5</td>
<td>M</td>
<td>Unexplained collapse of right lung</td>
<td>Asymptomatic</td>
<td>Chest x-ray CT scan Bronchoscopy</td>
<td>Positive</td>
<td>Null</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Pavlov (2013)</td>
<td>13</td>
<td>F</td>
<td>Stertorous breathing Wheezing</td>
<td>Asthma attack</td>
<td>Chest x-ray Pulmonary function test Fiberoptic bronchoscopy</td>
<td>Positive</td>
<td>NS</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>Zhang (2012)</td>
<td>16</td>
<td>NS</td>
<td>Cough x1 month Fever Night sweat x6 months Weight loss</td>
<td>N5</td>
<td>CT scan Fiberoptic bronchoscopy Bronchial brushings Chest x-ray</td>
<td>Positive</td>
<td>Weakly positive for CDS &amp; CD3</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>20</td>
<td>Chen (2008)</td>
<td>17</td>
<td>M</td>
<td>Chronic dry cough Low grade fever x6 wk Weight loss</td>
<td>Tuberculosis</td>
<td>Chest x-ray Chest CT Flexible bronchoscopy</td>
<td>NS</td>
<td>NS</td>
<td>Generalized lymphadenopathy</td>
</tr>
<tr>
<td>3</td>
<td>Guerra (2006)</td>
<td>9</td>
<td>F</td>
<td>Dry cough x3 months Chest pain Dysnea Low-grade fever</td>
<td>Acute bronchospasm</td>
<td>Chest x-ray CT scan Fiberoptic bronchoscopy &amp; biopsy</td>
<td>Positive</td>
<td>T-cell</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>Bhalla (2003)</td>
<td>17</td>
<td>F</td>
<td>Progressive dyspnea x2 weeks</td>
<td>N5</td>
<td>Chest x-ray CT scan Bronchoscopy Bronchial washings Biopsy</td>
<td>Positive</td>
<td>T-cell</td>
<td>None</td>
</tr>
<tr>
<td>21</td>
<td>Huang (2004)</td>
<td>15</td>
<td>M</td>
<td>Right neck mass x1 month Dyspnea Hemoptysis Subcutaneous emphysema</td>
<td>Post-obstructive pneumonia</td>
<td>CT scan Echo-guided biopsy (cervical lymph node) Bronchoscopy</td>
<td>Negative</td>
<td>T-cell</td>
<td>Cervical lymph node</td>
</tr>
</tbody>
</table>

NS, not specified.

This table annotates in chronological order all cases of pediatric endobronchial ALCL restricted to the English language as available on PubMed and Medline. Purple ‘highlighted’ cases are those that were isolated to the endobronchium with no evidence of extrapulmonary involvement [2,3,13].
raised LDH levels, and the presence of a mediastinal mass are other presenting symptoms [10]. Children with ALCL may have an indolent phase characterized by mild lymphadenopathy with fewer prior to progression. Endobronchial ALCL typically presents with dyspnea and atelectasis of the distal parenchyma [11]. Plastic bronchitis caused by neoplastic infiltrates originating from an ALCL has also been reported in a seven-year-old girl under investigation for refractory pneumonia [12]. Over half of all ALCL patients present with stage III/IV and have systemic symptoms. Extralodal disease is present in 40–50% of cases [2]. The presentation of NHLs as endobronchial neoplasms is extremely rare.

On immunohistochemical (IHC) staining, ALCL cells are positive for CD30, CD45, EMA, and B宁H9. Expression of T-cell antigens including CD2 and CD4 is common, with CD43 expression in 2/3 of cases [13]. The T-cell markers CD3 and CD45RO may be negative in >50% of cases [8]. Thus, the use of limited immunohistochemical panels can potentially lead to confusion of ALCL with other neoplasms as seen in our index case. Additionally, approximately 70–80% of ALK+ ALCLs express CD99, an antigen also present in Ewing’s sarcoma. Further, as ALCLs can be of the null phenotype with no expression of routine T- and B-cell markers, this remains a common diagnostic pitfall for “Ewing’s sarcoma” as seen in our case and can only be ascertained by a high index of clinical and pathological suspicion [14]. Such distinction is extremely important as the primary treatment of a malignant endobronchial tumor is surgical whereas in lymphoma, chemotherapy remains the gold standard.

ALCL in children responds well to chemotherapy, with the majority entering complete remission. However, recurrence rates may be as high as 39–81% and predominantly occur within months of treatment completion [3]. The 5-year survival rate is 79.8% for ALK positive disease, and 32.9% for ALK negative disease [11]. ALK-positive ALCL tumors have a higher frequency of extranodal involvement than ALK-negative tumors [15]. The most significant prognostic factor for children with ALCL is ALK positivity, which is associated with a good therapeutic response and longer overall survival [16].

While pulmonary involvement of ALCL occurs as a result of dissemination in 12% of all cases, primary endobronchial ALCL is extremely rare [1]. The first case of endobronchial ALCL without disseminated disease was described by Guerra et al. in 2006 [3]. Due to the rarity of these lesions, guidelines for management are largely consensus-based rather than evidence-based and the optimal therapy still remains to be determined.

Reviews of large series of CD30+ ALCL in 225 [17], 82 [18], and 32 [19] children revealed no reported cases of isolated endobronchial ALCL. Though NHL presenting as an endobronchial tumor has been reported in the adult population, to the best of our knowledge, only three case reports have described primary, isolated endobronchial ALCL in the pediatric English literature [2,3,13]. These patients were aged 9 (female), 13 (female), and 17 (female). Our case is therefore the first report of a male with this diagnosis, as well as the youngest patient. Table 1 is a comprehensive list of pediatric endobronchial ALCLs as reported in the English literature [2,3,11,13,20,21].

3. Conclusion

On clinical grounds, ALCL is a relatively infrequent tumor. Endobronchial lesions in NHL are the rarest intrathoracic manifestation of ALCL even in advanced widely disseminated disease. In this context, this case of isolated endobronchial presentation of ALCL remains a rarity and an exceedingly uncommon event. Though histopathology is the primary tool to differentiate ALCL from other benign and malignant endobronchial lesions, it is important to be aware of the diagnostic pitfalls of the ‘null phenotype’ ALCL, which is negative to routine T- and B-cell markers. In summary, such lesions, due to their rarity and complexity remain diagnostic challenges that necessitate a high degree of clinical suspicion for accurate identification to guide early appropriate treatment.

Conflict of interest statement

The authors declare no conflict of interest.

References