Primary Endobronchial Anaplastic Large Cell Lymphoma in a Pediatric Patient

JHON GUERRA, MD*; MARIA ECHEVARRIA-ESCUDERO, MD *; NILKA BARRIOS, MD*; ROMAN VELEZ-ROSARIO, MD†

The authors describe a pediatric patient who presented with a 3-month history of dry cough, chest pain, progressive breathlessness, fever and recurrent pneumonia with atelectasis. A fiberoptic bronchoscopy revealed a whitish lesion at the left bronchus. A biopsy of the lesion demonstrated an anaplastic large cell lymphoma (ALCL). Evaluation for disseminated disease was negative. After the patient completed chemotherapy the lesion abated and she has been in complete remission for almost 4 years. Although extranodal involvement of ALCL is frequent at some stage of the disease, endobronchial involvement is extremely rare even in the presence of advanced disease. To our knowledge, this is the first primary isolated endobronchial ALCL described in a pediatric patient.

Key words: Primary Endobronchial Lymphoma, Childhood

Case Report

A 9-year-old girl with a negative history of significant medical illnesses, presented at the University of Puerto Rico Pediatric Hospital with the complaint of persistent dry cough of 3 months of duration, chest pain, breathlessness and intermittent low grade fever. The patient had visited her primary physician in four previous occasions with these symptoms. She was diagnosed with acute bronchospasm each time, and was treated initially with β-2-adrenergic agonists and leukotriene receptors antagonist without improvement. The chest radiograph revealed a left upper lobe lingular segment opacification and she was treated with antibiotics for 10 days for suspected pneumonia with associated atelectasis without response. Computed Tomography (CT) of the chest was done and revealed a 9.0 cm x 6.5 cm x 12 cm hypodense left upper lobe mass, with necrosis that encased the left hilum (Figure 1). A fiberoptic bronchoscopy was done confirming airway obstruction, and revealing a whitish round mass adhered to the antero-lateral wall at the lower third of left main bronchus (Figure 2). Section of the endobronchial biopsy (Figure 3) examined in our institution and reviewed by AFIP (Armed Forces Institute of Pathology), demonstrated a dense proliferation of discohesive anaplastic cells with enlarged round to pleomorphic nuclei with abundant cytoplasm. Immunohistochemical studies of the tumor cells were positive for LCA, CD30, ALK1, CD43, TIA-1 and CD7 and negative for Pan-keratin, CD3, CD20, CD99, CK7, CK20, chromogranin, synaptophysin, NCAM (CD56), S100, TTF1 and mucicarmin skin, which was interpreted as indicators

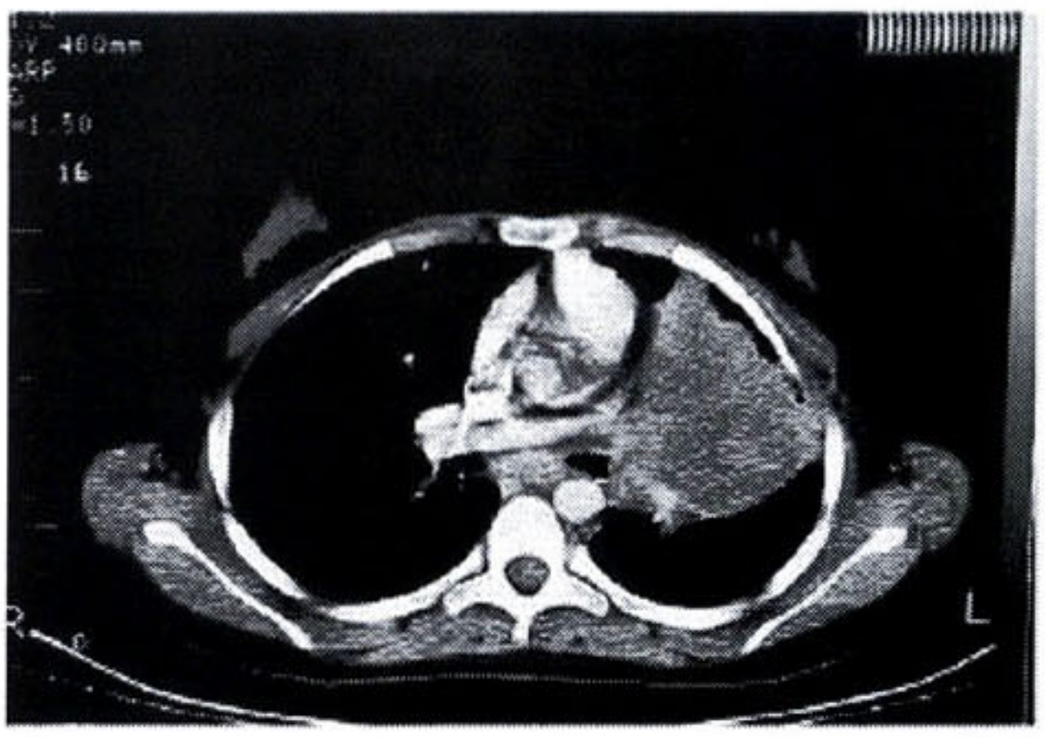

Figure 1. Chest Computed Tomography Scan shows a left upper lobe mass with increase areas of necrosis and encasement of the left hilus.

*Departments of Pediatrics and †Pathology, University of Puerto Rico School of Medicine

Address correspondence to: Dr. Jhon Guerra, Department of Pediatrics, Hematology-Oncology Section, University of Puerto Rico School of Medicine, GPO Box 365067 San Juan, PR 00936 5067. Fax: (787) 751-5812 E-mail: jhonguerra@wartech-pro.com

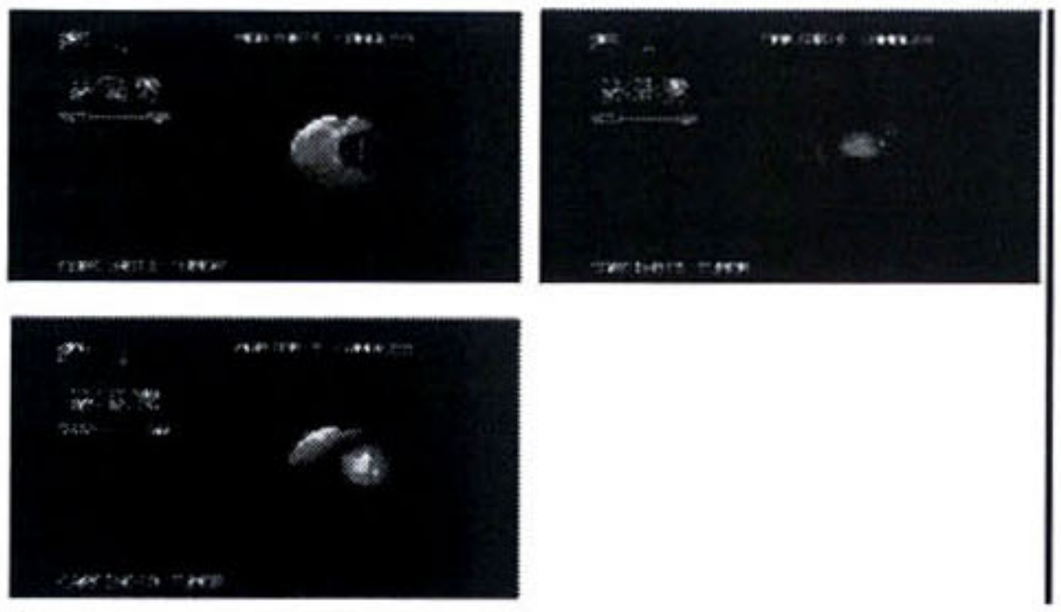

Figure 2. (A)(B)(C) Endobronchial bronchoscopy sequence demonstrates a whitish round mass in the left main bronchus

of an histological diagnosis of anaplastic large cell lymphoma (ALCL) CD30+ and ALK1+, T-cell type. Remarkable laboratory findings included high lactate dehydrogenase (LDH) levels and sedimentation rate, elevated concentrations of immunoglobulin M and slightly low levels of immunoglobulin G. There was also evidence of past CMV infection, but negative EBV and HIV Elisa titers. These results are presented in table 1. Bone marrow aspiration and biopsy showed normal marrow elements

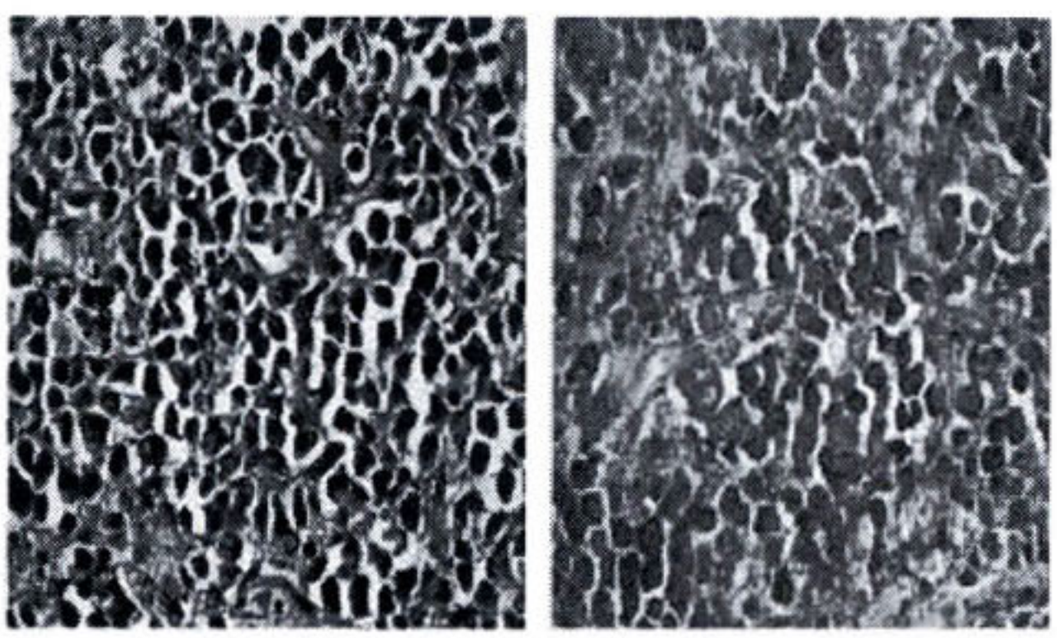

Figure 3. (A) Diffuse proliferation of large cells with irregular nuclei, some of them showing eccentric kidney shape nuclei. (B) Malignant cells are positive for CD30.

without foreign cells involvement, with both normal immunophenotyping and genetic studies. Additional evaluation done to evaluate for disseminated disease,

Table 1. Results of the Laboratory Tests

Parameter	Patient	Normal Range
Lactate Dehydrogenase	443	110-215 U/L
Immunoglobulin M	787	63-287 mg/
dlImmunoglobulin G	689	723-1685 mg/
dlSedimentation Rate	86	0-20 mm/
hrCytomegalovirus IgG	106.9	0-10 IU/ml

which included cerebrospinal fluid analysis, CT of the abdomen, CT of the pelvis and bone scientigraphy, were negative. Whole body gallium scan revealed a large gallium avid lesion in the left hemithorax. She received induction chemotherapy with vincristine, prednisone, doxorubicin, and intrathecal methotrexate. Following induction chemotherapy, she was evaluated with Chest CT Scan and it revealed minimal residual disease of left hilum and left upper lobe. Her follow up Gallium Tomography (SPECT) was reported as normal. Maintenance chemotherapy for a total of 15 cycles given at 3-weeks intervals was followed. It consisted of 5 cycles of doxorubicin, vincristine, 6-Mercaptopurine and prednisone, followed by 10 cycles with methotrexate substitution as a single intravenous dose. In addition, she also received intrathecal methotrexate on day 1 of cycles 1, 3, and 5 of maintenance schedule. The patient completed the chemotherapy treatment course of 12 months on December 2001, and has been in complete remission for almost four years.

Discussion

Childhood Non-Hodgkin's lymphoma (NHL) is classified in four major pathological subtypes based on the histology. The distribution of these subtypes includes 40% Burkitt lymphoma, 20% diffuse large cell lymphoma, 30% lymphoblastic lymphoma, and 10% anaplastic large cell lymphomas (1). The cellular origin is usually of B or T phenotype. In ALCL, however the cell of origin is different (2). They represent a distinct category of large cell lymphomas defined by a strong expression of high levels of Ki-1 that subsequently was designated as CD30 antigen (3). Three subtypes of ALCL have been recognized. These include primary systemic ALCL with positive ALK, primary systemic ALCL with negative ALK, and primary cutaneous ALCL (3). The establishment of definitive characteristics of such subtypes in the pediatric population has been complex due to the small number of cases, and the absence of a shared staging system (4,5). In comparison to other childhood non Hodgkin's lymphomas, the most common areas of involvement are lymph nodes (peripheral, intrathoracic, and intra-abdominal), usually associated with mediastinal involvement and hepatosplenomegaly. Other sites include skin, bone, muscle, and lung parenchyma. Childhood ALCL infrequently comprise the bone marrow or central nervous system (6). Endobronchial NHL involvement is extremely rare but has been described in adolescents with disseminated NHL (7). To our knowledge, primary endobronchial ALCL without disseminated disease or clear site of origin, as seen in this pediatric case, has never been reported. There are only very few

cases reported in adults (8,9) and one in a late adolescent girl (10) where endobronchial ALCL is the primary site involved. The French Society of Pediatric Oncology performed a multivariate analysis in patients with ALCL and found that mediastinal and/or visceral involvement, and a LDH level above 800UI/L are associated with an increased risk of treatment failure. On the other hand, their absence is associated with a higher rate of complete remissions (11). The Berlin-Frankfurt-Munster (BFM) group studies ALCL individually and it is treated based on the patient's risk category. Patients with low risk factors are treated with short (2-5 month) intensive chemotherapy whereas the high risk patients are treated with more prolonged chemotherapy (12). Others consider ALCL as part of NHL and use a staging system according to the initial disease extension. They treat patients with the same chemotherapy protocols for NHL disregarding histology subgroup or immunophenotype (13,14). Childhood ALCL responds well to chemotherapy and complete remission after the induction regimen is easily achieved, however, recurrence rates are high, ranging from 39 to 81% [11]. These relapses appear within few months after completion of treatment. The optimal therapy remains to be determined. In our case the disease was localized, without evidence of extension and with a lactate dehydrogenase level <800 IU/L. The duration of the treatment was 12 months and it was well tolerated. In conclusion, pulse cycles of chemotherapy over a 12 month period, without local therapy modalities, were effective in the treatment of this child with Ki-1 ALCL. Although endobronchial NHL is very rare, it should be considered in a patient with persistent cough, atelectasis and recurrent pneumonia and, a bronchoscopy examination is recommended if there is no clinical improvement with adequate treatment.

Resumen

Los autores describen un paciente pediátrico quien presentó con clínica de 3 meses de evolución de tos seca, dolor de pecho, dificultad respiratoria progresiva, fiebre y neumonía recurrente con atelectasias. La broncoscopía de fibra óptica reveló una lesión blanquecina en el bronquio izquierdo. La biopsia de la lesión demostró un Linfoma Anaplásico de Células Grandes y la evaluación para enfermedad diseminada fue reportada negativa. Después de completar quimioterapia la lesión desapareció y la paciente ha permanecido en remisión completa por cerca de 4 años. Aunque el compromiso extranodal del Linfoma Anaplásico de Células Grandes es frecuente en algún momento durante su curso, el envolvimiento endobronquial es extremadamente raro aún en presencia de enfermedad avanzada. A nuestro entender, este es el primer caso aislado de Linfoma Anaplasico de Células Grandes endobronquial descrito en un paciente pediátrico.

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