

# UNSUSPECTED LUNG PATHOLOGY IN AUTOPSIES OF CHILDREN WITH CANCER

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## ABSTRACT

**Background:** Although pulmonary involvement is common in patients with cancer, its frequency and nature is seldom reported in the medical literature. **Objective:** To determine the frequency and type of lung pathological conditions revealed by autopsy in children with cancer. **Methods:** All reports from autopsies performed in children with cancer from 1989 to 2012 in a pediatric hospital were reviewed. **Results:** In the analyzed period, 118 autopsies (10.2% of all autopsies) corresponded to children who died with cancer; 76 had complete information and were included in the analysis. Children were seen in the Hematology (41 cases) or the Oncology (35 cases) services. Their median age at decease was 7 years (range, 15 days to 16.1 years) and 46.1% were females. Main diagnoses were acute lymphoblastic (31 patients) or myeloblastic (10 patients) leukemias and tumors of the central nervous system (12 patients). A pathological respiratory condition was diagnosed antemortem in 31 (40.8%) patients, and at autopsy in 62 (81.6%) cases. Omitted diagnoses occurred in 58 (76.3%) children, being pneumonia (24 cases) and pulmonary hemorrhage (23 cases) the most frequent omissions. Nine patients had clinically unsuspected tumor infiltration or metastases. **Conclusions:** In these children with cancer, more than 80% of autopsies revealed some lung pathology, mainly of infectious or hemorrhagic nature. Thus, pulmonary involvement should be investigated in all children with cancer in a timely and intentional manner. (REV INVES CLIN. 2017;69:28-32)

**Key words:** Cancer. Lung pathology. Autopsy. Necropsy.

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## INTRODUCTION

In the last decades, a declining trend in the rate of autopsies performed has been observed worldwide. However, there is ample evidence that the autopsy is a relevant source of diagnostic information and a learning tool for future cases. In addition, autopsies allow the evaluation of diagnostic accuracy (and therefore, assessment of the quality of hospital services), help to identify differential diagnoses, unveil unsuspected conditions, and evaluate the impact of therapeutic measures<sup>1-8</sup>. Cancer is one of the diseases in which the autopsy yields more benefits, either for research or for the improvement of medical care<sup>9-12</sup>. A number of published studies have reported autopsy findings in children with cancer, but the majority of them are focused primarily on clinical-pathological inconsistencies, causes of death, omitted diagnoses, unexpected findings, or infectious complications<sup>13-15</sup>. Although the lung is one of the most frequently affected structures in patients with cancer, the medical literature concerning pulmonary involvement in pediatric patients with cancer is scarce<sup>10,12,16</sup>. Thus, the objective of the present study was to investigate the frequency and type of lung pathology revealed by autopsies in children with cancer.

## PATIENTS AND METHODS

This was a retrospective study performed in a tertiary-level pediatric hospital. Reports of autopsies performed from January 1989 to December 2012 in children under 17 years of age, and with a diagnosis of cancer were analyzed. Due to the large time-period analyzed, complete clinical charts could not be obtained in all patients, and thus relevant data was also obtained from death notes, death certificates, and autopsy reports. From these sources of information, each case was jointly evaluated by the medical team that was responsible for the patient and the Mortality Committee (integrated by nine specialists in pediatrics, hematology, oncology, critical care medicine, pulmonary medicine, and pathology). From these evaluations, we elaborated an ad-hoc database. The analyzed variables were demographic data, type of cancer, all clinical diagnoses established by clinicians including suspected pulmonary involvement, histopathological findings regarding lung pathology at autopsy, and omission of diagnoses of respiratory diseases and whether they were potentially treatable. Data were analyzed with descriptive statistics.

## RESULTS

During the study period, 1162 autopsies were performed in the hospital, with 118 (10.2%) corresponding to patients with cancer. Complete data could be obtained from 76 cases and they were included in the present analysis. Forty-one patients (53.9%) were seen in the Hematology service, where they were diagnosed with acute lymphoblastic leukemia (31 patients) or acute myeloid leukemia (10 patients). The remaining 35 patients (46.1%), were seen by the Oncology service, being tumors of the central nervous system the most frequent diagnosis (Table 1). The median age of the population was 7 years (range, 15 days to 16.1 years), and 46.1% were females. In patients with hematological disorders, the main diagnosis at autopsy always derived from the clinical diagnosis; thus, in these patients the agreement between both diagnoses was 100%. In turn, in patients with non-hematological cancer, the clinical-autopsy concordance of the main diagnosis was 88.6%, since the diagnosis at autopsy was different in 4 out of 35 patients. These 4 discordant cases had clinical diagnoses of neuroblastoma, subependimal astrocytoma, meningeal tuberculosis, and primitive neuroectodermal tumor. However, the autopsies revealed that in fact they corresponded to non-Hodgkin lymphoma with dissemination to lumbar spinal canal and brain; right frontal primitive neuroectodermal tumor extended to the right lateral ventricle, nucleus caudalis, corpus callosum and left frontal lobe; central nervous system primary lymphoblastic lymphoma with leptomeningeal infiltration; and a well-differentiated neuroblastoma, respectively.

Regarding the cause of death, in 5 patients with septic or mixed shock, the anatomicopathological cause of death could not be determined by autopsy. In the remaining 71 patients, the clinical-autopsy concordance on the cause of death was 69%.

### Respiratory findings at autopsy

At the time of death, 31 (40.8%) patients had one or more clinical diagnoses of lung involvement mentioned in any of the documents we used to obtain the information, contrasting with the total number of 62 (81.6%) patients with some lung pathology discovered during the autopsy. The main respiratory findings at autopsy are shown in table 2.

Table 1. Anatomopathological diagnosis of the pediatric oncology patients (35 cases)

Topography or diagnosis	Number (%)	Diagnosis (Number)
Central nervous system	12 (34.2)	Anaplastic astrocytoma, brain stem (2) Glioblastoma (2) Anaplastic ependymoma (1) Myxopapillary ependymoma (1) Gangliocytoma (1) Germinal (1) Pineal anlage tumor (1) Primitive neuroectodermal tumor (1) Atypical teratoid/rhabdoid tumor (1) Lymphoblastic lymphoma (1)
Lymphoma	7 (20)	Hodgkin (2) Lymphoblastic lymphoma (1) Hemophagocytic syndrome (1) Large cells (2) Angiocentric (1)
Adrenal gland	2 (5.71)	Neuroblastoma
Sympathetic chain	2 (5.71)	Neuroblastoma
Soft tissue	4 (11.42)	Parameningeal rhabdomyosarcoma (1) Mediastinal primitive neuroectodermal tumor (1) Mediastinal malignant Schwannoma (1) Retroperitoneal malignant mesenchymoma (1)
Bone	3 (8.57)	Osteosarcoma
Liver	2 (5.71)	Hepatoblastoma
Kidney	2 (5.71)	Nephroblastoma
Biliary ducts	1 (2.8)	Rhabdomyosarcoma

Table 2. Respiratory diagnoses made at autopsy in 76 children who died with cancer

Pneumonia	30 (39.5)	Metastases	3 (3.9)
Pulmonary hemorrhage	30 (39.5)	Diffuse alveolar damage	3 (3.9)
Tracheobronchitis	13 (17.1)	Atelectasis	3 (3.9)
Pulmonary edema	9 (11.8)	Pulmonary thromboembolism	2 (2.6)
Tumor infiltration	6 (7.9)	Pulmonary infarction	2 (2.6)
Pleural effusion	5 (6.6)	Other	6 (7.9)
Hemothorax	3 (3.9)		

Data correspond to number (percentage) of patients with the diagnosis.

Omitted diagnoses (*i.e.*, pathological abnormalities discovered at autopsy but not mentioned in the clinical chart, death note or death certificate) occurred in 58 (76.3%) children, being pneumonia (24 cases) and/or pulmonary hemorrhage (23 cases) the most frequent diagnoses found in 40 (52.6%) patients. From the 76 patients included in the study, it was possible to analyze 70 to decide whether or not their pulmonary involvement was potentially treatable. In 35 (50%) patients, the attending medical team and the Mortality Committee decided that the complication was treatable.

It is worthy to note that the autopsy detected tumor infiltration in 6 patients and metastases in other 3 patients, all of them clinically unsuspected. These complications occurred in 5 children with leukemia, 2 children with Hodgkin's lymphoma, and 2 children with osteosarcoma. In addition, from the 6 children with tumor infiltration, 2 also had pulmonary hemorrhage, 2 had pneumonia (potentially treatable), and 1 had both processes.

At the time of their last hospital admission, there were 3 patients in terminal stage and 1 in premortem

condition. Only in one of them the pulmonary complication (herpes virus pneumonia) was considered treatable.

## DISCUSSION

Technological advances in diagnostic procedures have not diminished the value of the autopsy. In 2010, Scordi-Bello et al.<sup>17</sup> found similar rates of clinical-pathological discrepancy in three clinical settings that differed in the amount of antemortem diagnostic workup, thus refuting the hypothesis that the availability of diagnostic procedures decreases the frequency of discrepancies in the diagnosis. A systematic review by Shojania et al.<sup>2</sup> concluded that the capacity of the autopsy to identify diagnoses unsuspected before death is high enough as to reinforce the recommendation of performing autopsies.

The autopsy continues to be well recognized as a source of relevant medical information (accuracy of diagnoses, discovery of unexpected findings, feedback regarding therapeutic outcome, etc), a tool for learning, and a measure of quality control. In public health, it is an indicator of the behavior of health systems through time, and allows comparisons between them<sup>1,3-6,11,15,17-21</sup>. In spite of this, specifically in pediatric patients with oncological diseases, the usefulness of the autopsy has been questioned because the main diagnosis, *i.e.*, the malignant disease, was fully corroborated (for example, by biopsy) when the patient was still alive. This belief explains the low percentage of autopsies performed in children with hemato-oncological diseases, as has been noted in case-series reports. For example, Buckner et al.<sup>15</sup> analyzed 533 autopsies performed in a 20-year period, and they found that only 43 cases (8.06%) had a main diagnosis of neoplasia, with 25.6% of misdiagnoses and 23.3% of omitted diagnoses. These authors concluded that the autopsy continues to provide previously unknown diagnostic information and remains a valuable tool for pediatricians and pediatric oncologists. This last conclusion has been confirmed in a number of studies showing that main diseases have a clinical-pathological discordance between 15% and 53%<sup>2,4,6,9,13-17</sup>.

The autopsy can provide unexpected information even in children dying due to end-stage cancer, and hence the procedure is still advisable<sup>15</sup>. Moreover, the complexity of the disease may lead to a delay or omission

of some diagnoses, mainly during exacerbations or at the end-stage of the disease<sup>10</sup>. In spite of this evidence, little emphasis has been made on respiratory comorbidities, which are among the most frequent clinical causes of death in these patients.

Acute or chronic pulmonary complications in patients with current or past cancer are well characterized in the medical literature, both in children and adults<sup>12,22-26</sup>. These complications are diverse and include infections, fibrosis, diffuse alveolar hemorrhage; tumor infiltration, metastases, atelectasis and vascular or hemorrhagic conditions such as vascular leakage with edema and infarction, hemorrhage, pulmonary thromboembolism, etc.<sup>10,12,16,22,27</sup>. In contrast, their participation and magnitude in the autopsy of patients with cancer are scant and unspecific<sup>10,11,13,16</sup>.

In the present study, pulmonary involvement was very frequent, since more than half of the patients presented pneumonia and/or pulmonary hemorrhage, which can be explained by the immunosuppression and the hematological abnormalities due to the disease and treatment<sup>27</sup>. All the pulmonary manifestations mentioned in the medical literature were found in our population, such as vascular-hemorrhagic pathologies (pulmonary edema, thromboembolism or infarction) and tumoral activity (infiltration and metastases). Lung infection and bleeding were the two most conditions most frequently overdiagnosed, but most importantly, these were also the two most frequently omitted diagnoses in up to 52.6% of the cases. Some patients had both conditions, but 17 cases only had pneumonia, which could be potentially treatable, thereby increasing the chances of the patient's survival.

Another relevant finding in this series was tracheobronchitis associated with mechanical ventilation. This condition is considered as a precursor of ventilator-associated pneumonia and its presence is an indication for antibiotic and antiinflammatory therapy, which could prevent its evolution into a pneumonic process and avoid a fatal outcome<sup>28</sup>. Tracheobronchitis is usually an endoscopic finding during bronchoscopy in patients in critical condition. The clinical and laboratory data suggestive of this condition are fever, sputum production, leukocytosis or leukopenia, and the absence of a new or progressive radiographic lung pattern. These signs must alert the clinicians in order to initiate a timely and specific treatment, preferentially based on microbiological

results from sputum or bronchoalveolar lavage samples, in an attempt to avoid progression of the disease to distal airways.

A potential limitation of this retrospective study was that a relatively large number of patients who died with cancer (42 out of 118) could not be included in the study. The main reason for this loss was that the sources of information (clinical records, death note, death certificate, and autopsy report) did not contain enough relevant data on key variables of the study. However, even with this drawback, we consider that the number of children included in our study was high and the analysis yielded important information about pulmonary involvement in patients with cancer. In this context, our results revealed that a high percentage of lung pathologies occurred in patients with neoplastic diseases, mainly pneumonia and/or pulmonary hemorrhage, and that they frequently contributed to the patient's worsening and death. This finding should alert clinicians to begin preventive measures, have a high degree of suspicion of tracheobronchitis in patients under mechanical ventilation, and intentionally include the search for respiratory infection or hemorrhage into the workup of worsening episodes in these patients. Further studies are needed to corroborate our results.

## CONFLICT OF INTEREST

All authors were members of the former Mortality Committee, chaired by Dr. María Elena Y. Furuya.

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