

**Clinical Case Seminar**

**CCS1(1-6)**

# **Mediastinal Mass and Pleural Effusion: different clinical presentations of lymphoma in pediatric age.**

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## **Abstract**

**Background:** Mediastinal masses and pleural effusions may have different etiologies, from infectious to malignant and autoimmune diseases, originating from the mediastinum or nearby structures. Several signs and symptoms, such as persistent anemia, dyspnea, chronic itching, and mantle oedema, may raise suspicion of a malignant disease. Specifically, lymphomas may be a common cause of both mediastinal masses and pleural effusions.

**Case presentation:** We report the cases of two children, aged 9 and 13, who were admitted to the Pediatric Unit of AOU “Gaetano Martino” in Messina with pleural effusion and superior vena cava syndrome, respectively. Both had a previous history of SARS-CoV-2 infection a few months prior. Clinical, laboratory and radiological findings suggested the presence of a mediastinal mass, compatible with lymphoma.

**Conclusions:** Tumors are a rare clinical entity in pediatric age. These cases highlight the importance of an accurate diagnostic workup and the critical role of identifying red flags. Nowadays, precision medicine plays a fundamental role as it uses the knowledge of genetic and biochemical profiles of a disease to tailor diagnosis and therapy for pediatric patients with tumors.

**Keywords:** lymphoma; leukemia; mediastinal mass; pleural effusion; precision medicine.

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## **Introduction**

Onco-hematological tumors represent a complex group of diseases in pediatric age, with a significantly increasing incidence over the past two decades [1].

Mediastinal tumors are predominantly malignant and occur less frequently in children than in adults [2].

The most common malignant tumors include lymphomas, neuroblastomas, and germ cell tumors, while the most common benign lesions include thymic cysts, teratomas, and bronchogenic cysts [3].

According to the location, mediastinal masses are categorized into three compartments: anterior mediastinum (malignant: lymphomas, germ cell tumors and thymomas; benign: thymic cysts and teratomas), middle mediastinum (malignant: lymphomas and metastases; benign: bronchogenic cysts and pericardial cysts) and posterior mediastinum (malignant: neuroblastomas and Ewing sarcoma;

benign: neurofibromas and ganglioneuromas) [3].

Many mediastinal masses are asymptomatic and discovered incidentally, whereas symptoms depend on size, location, and compression effects [3]. While benign lesions have an excellent prognosis after surgery, malignant tumors vary depending on the type [3].

Lymphoma, a solid tumor originating from lymphocytes within lymph nodes, may arise in the mediastinum and spread through various pathways, including blood and lymphatic vessels, involving organs such as the bone marrow, spleen, and non-lymphatic sites, such as the skin, lungs, central nervous system, stomach, and liver [2]. Most cases occur with breathing difficulty, productive cough, pleural and/or pericardial effusion, superior vena cava (SVC) syndrome, neck masses, airway compression, fever, and chest pain [2].

Lymphomagenesis results from a complex interaction between genetic factors and different stressors, involving a clonal proliferation of B-cell, T-cell, and natural killer (NK) cell subsets of lymphocytes at different stages of maturation [4]. There are two main categories: Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL) [4]. HL is characterized by the presence of pathological Hodgkin Reed-Sternberg (HRS) cells, which originate from B-cells, within a background of nodular sclerosis, lymphocyte predominance, or depleted stroma [4]. Conversely, NHL, the more aggressive type, lacks HRS cells [4].

Accurate diagnosis in oncology requires a comprehensive knowledge of signs and symptoms, and the ability to promptly recognize them, as this greatly influences prognosis [5]. Predicting respiratory complications in mediastinal masses involves evaluating various clinical factors such as age, gender, pathological diagnosis, and key symptoms, including cough, dyspnea, hypoxia, orthopnea, chest pain, wheezing, SVC syndrome, and stridor [5]. Laboratory tests, including tumor markers (serum soluble IL-2 receptor,  $\alpha$ -fetoprotein, human chorionic gonadotropin, and neuron-specific enolase), along with radiological assessments (chest computed tomography (CT) and X-ray) are crucial for diagnosis [5].

In the rapidly advancing field of precision medicine, technologies like Next-Generation Sequencing (NGS) are improving our knowledge of the genetic and biochemical profiles of diseases, thereby enabling tailored treatments [6]. This evolving diagnostic and therapeutic approach is significantly impacting pediatric oncology [6].

Here, we describe two pediatric cases of lymphoma with different clinical presentations.

## **Case Presentation**

### **Case I**

A 9-year-old Caucasian male, with a silent medical history, was admitted to the Pediatric Unit of AOU “Gaetano Martino” in Messina due to fever. Several weeks before, he had experienced right

hip pain, without fever, along with mild dyspnea. He had also previously contracted SARS-CoV-2 infection. The thoracic auscultation revealed respiratory silence in the right hemithorax. Initial laboratory investigations revealed a markedly elevated Lactate Dehydrogenase (LDH) and C-Reactive Protein (CRP) levels (Table 1).

**Table 1.** Results of patient’s laboratory test.

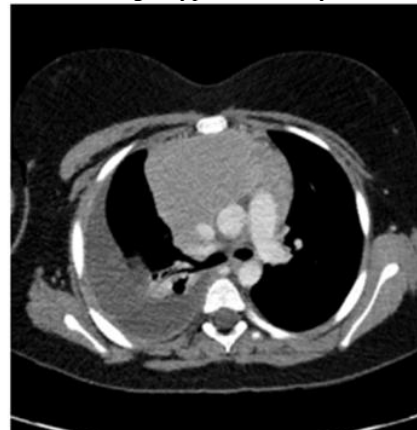
|                           | <b>Laboratory parameters</b> | <b>Patient’s values</b> |
|---------------------------|------------------------------|-------------------------|
| <b>Hospital admission</b> | Red Blood Cell count         | 4850000/mmc             |
|                           | Hemoglobin                   | 12.8 g/dl               |
|                           | White Blood Cell count       | 11800/mmc               |
|                           | Neutrophilic count           | 5192/mmc                |
|                           | Lymphocytic count            | 6018/mmc                |
|                           | Platelet count               | 297000/mmc              |
|                           | Lactate dehydrogenase        | 6 x N                   |
|                           | C- Reactive Protein          | 21 x N                  |

A chest X-ray showed nearly complete opacification of the right hemithorax (Figure 1), while lung ultrasound confirmed extensive pleural effusion with associated atelectasis. Pleural effusion related to infective pneumonia was suspected, so empirical antibiotic therapy with meropenem and amikacin was started. However, after one day, the patient developed tachypnea and oxygen desaturation, requiring oxygen therapy. A thoracentesis was performed, and the hemorrhagic serous effusion was sent for cultural, cytological and immunohistochemical analysis. A chest CT scan revealed a large, well-defined hypodense mass measuring 9 x 7 cm in diameter (Figure 2).

**Fig. 1.** Chest X-ray showing a massive pleura effusion in the right hemithorax.



**Fig. 2.** Chest Computed Tomography scan showing a hypodense bulky mass.



A bone marrow aspiration was also performed, confirming the diagnosis of T-cell acute lymphoblastic leukemia/lymphoma. The patient was then transferred to the Oncohematology Unit of AOU “Gaspare Rodolico” in Catania to receive appropriate therapy.

**Case II**

A 13-year-old Caucasian girl was admitted to the Pediatric Unit of AOU “Gaetano Martino” with a clinical presentation characterized by generalized itching and progressive weight loss (>10 kg)

following a SARS-CoV-2 infection seven months earlier, in March 2022. No history of persistent fever or night sweats were reported. In June 2022, she underwent a dermatological evaluation and was diagnosed with atopic dermatitis with impetiginized lesions. She was treated with amoxicillin, antihistamines, and oral corticosteroids. However, by July 2022, despite treatment, there was no improvement, so laboratory investigations were carried out, revealing anemia, neutrophilic leukocytosis, thrombocytosis, and elevated levels of inflammatory markers (Table 2). This led to her admission to the Pediatric Unit. Her clinical presentation included periorbital edema, skin xerosis, scratching lesions, particularly on the limbs, and mantle edema, along with decreased appetite and fatigue. Laboratory investigations showed a further increase in inflammatory markers (Table 2).

**Table 2. Results of patient’s laboratory test.**

|                                  | Laboratory parameters          | Patient’s values |
|----------------------------------|--------------------------------|------------------|
| <b>Before hospital admission</b> | Red Blood Cell count           | 4870000/mmc      |
|                                  | Hemoglobin                     | 10.5 g/dl        |
|                                  | White Blood Cell count         | 20210/mmc        |
|                                  | Neutrophilic count             | 15763/mmc        |
|                                  | Lymphocytic count              | 2021/mmc         |
|                                  | Platelet count                 | 730000/mmc       |
|                                  | Erythrocyte sedimentation rate | 72/mmh           |
|                                  | C- Reactive Protein            | 16 x N           |
| <b>Hospital admission</b>        | Red Blood Cell count           | 4960000/mmc      |
|                                  | Hemoglobin                     | 11.4 g/dl        |
|                                  | White Blood Cell count         | 17800/mmc        |
|                                  | Neutrophilic count             | 14774/mmc        |
|                                  | Lymphocytic count              | 1780/mmc         |
|                                  | Platelet count                 | 615000/mmc       |
|                                  | Lactate dehydrogenase          | 5 x N            |
|                                  | Erythrocyte sedimentation rate | 120/mmh          |
|                                  | C- Reactive Protein            | 18 x N           |
| Ferritin                         | 226 ng/dl                      |                  |

The presence of mantle edema and itching raised suspicion of malignancy, leading to consideration of a mediastinal mass. A thoracic X-ray revealed a radiopaque antero-lateral mass in the superior mediastinum, compressing the trachea and the superior vena cava. A CT scan confirmed the findings, suggesting lymphoma (Figures 3 and 4). The girl was transferred to the Oncohematology Unit of AOU “Gaspare Rodolico” in Catania for a biopsy and to receive appropriate therapy.

**Fig. 3.** Chest X-ray showing a radiopaque mass in the right superior anterolateral mediastinum.



**Fig. 4** Chest Computed Tomography scan showing a heterogeneous mass measuring 81x75 mm.



## Discussion

The two cases described represent two different presentations of lymphoma, supporting the

importance of early diagnosis and treatment when signs and symptoms suggestive of neoplastic disease arise in pediatric patients.

Concerning mediastinal tumors, the involvement of specific mediastinal compartments may aid in the initial diagnosis: tumors in the anterior mediastinum raise suspicion of lymphoma or leukemia, those in the middle mediastinum suggest adenopathy from leukemia or lymphoma, and those in the posterior mediastinum are more indicative of neuroblastoma [7].

The first case report describes a patient with pleural effusion. Hemorrhagic malignant pleural effusion (HMPE) is a specific type of malignant effusion characterized by high levels of red blood cells ( $>100,000/\text{mmc}$ ) and hematocrit ( $>1\%$ ), indicating the presence of malignant cells in the pleural cavity [8]. Other types of pleural effusions may arise from mechanical complications such as bronchial obstruction, SVC syndrome, lymph node infiltration, or thromboembolism [8]. However, a definitive diagnosis requires aspiration and cytological or histological analysis of pleural fluid biopsy [8]. Several tumors associated with mediastinal masses may cause compression of the tracheobronchial tree and obstruction of lymphatic flow, leading to the development of pleural effusion [8].

According to Light's criteria, LDH aids in distinguishing between exudative and transudative pleural effusions [9]. Exudative effusion is characterized by a pleural protein-to-serum protein ratio  $> 0.5$ , a pleural LDH-to-serum LDH ratio  $> 0.6$ , and pleural LDH levels  $> 200$  U [9].

The second case report describes a patient with SVC syndrome, a condition commonly associated with leukemia or lymphoma [10]. It may represent a potential prognostic factor [10].

In pediatric patients with malignant mediastinal masses, tailored treatment is crucial, often involving a chemotherapy regimen [11]. This highlights the importance of a careful management.

Current research focuses on DNA sequencing of tumor biopsies to identify genetic and epigenetic alterations that promote cancer cell proliferation and survival [12]. Additional studies are investigating drugs designed to target specific mutations, moving away from standardized chemotherapeutic agents towards personalized treatments based on identified driver mutations in pediatric tumors [12].

Genomic testing involves NGS molecular analysis [13]. Specifically, hotspot testing examines alterations in exons or intron/exon junctions within a preselected panel of cancer-related genes, including known activating oncogenes and tumor suppressor genes [13]. Nowadays, the overall goal is to mitigate all known side effects and toxicity associated with chemotherapy [12]. Although the molecular characterization of pediatric cancers has not yet led to substantial improvements in outcomes, it provides valuable insights into tumor biology and prognosis [13].

## Conclusions

Tumors represent a rare clinical entity in pediatric age and can present with non-specific symptoms. A detailed knowledge of tumor-related signs and symptoms can help physicians to identify underlying malignant diseases. Advances in understanding molecular characteristics, along with the increased knowledge of epigenetics and proteomics, are enhancing our comprehension of tumor biology. This progress may enable oncologists to develop new strategies to improve the outcomes and quality of life of patients.

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