

## CASE REPORT

## Un unexpected pleural effusion in a pediatric patient in apparently good health

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10.56164/PediatrRespirJ.2023.27

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**ABSTRACT**

Pleural effusion (PE) occurs when fluid collects between the parietal and visceral pleura. This condition is a complication of pneumonia and pleuritis and can occur in 5-40% of cases. In children, the main aetiological agents involved are *S. pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Mycobacterium tuberculosis*. However, in a few cases, it represents an epiphenomenon of a disease that can affect other organs different from the lungs, such as onco-haematological diseases. Herein, we described a pleural effusion due to an acute lymphoblastic leukaemia.

**IMPACT STATEMENT:** This case presents a singular experience manifested in a paediatric patient with ALL who initially presented with a large and unilateral pleural effusion with the aim to highlight the importance of never underestimating the possibility of an unusual underlying cause.

**INTRODUCTION**

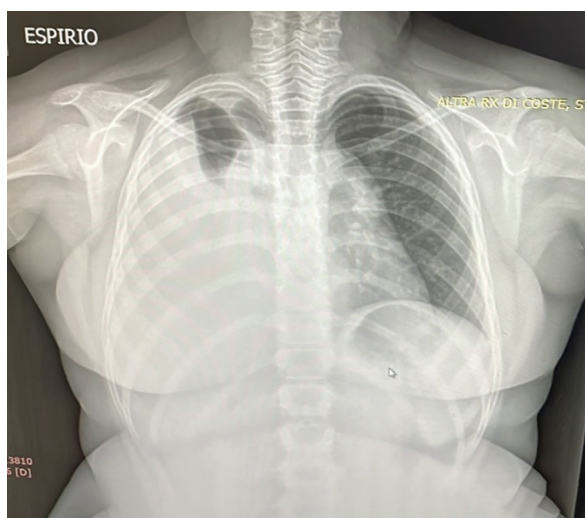
Pleural effusion (PE) occurs when fluid collects between the parietal and visceral pleura. The most common cause is infectious diseases; parapneumonic effusion complicates up to 13% of cases of pediatric community-acquired pneumonia, and sometimes hospitalization is required. The management of parapneumonic effusions remains disputed, and various therapeutic options are described (1). It is classified into two types: transudative and exudative effusions; the former does not have any specific diagnostic procedures or follow-up, whereas the presence of exudate necessitates further study.

**CASE REPORT**

We are describing the case of a 9-year-old male child who was first admitted to the Emergency Room of another hospital due to hip pain, shortness of breath and loss of appetite, following a four-day-history of tachycardia associated with right hip pain and no fever. The biochemical analyses and the chest X-ray (performed in this hospital) showed increased phlogosis indexes C-reactive protein (CRP) 106.3 mg/L 21xN; lactate dehydrogenase (LDH) 373 U/L, white blood cells (WBC) 11800 mmc, neutrophils (N) 44%, lymphocytes (L) 51%, platelets (PLT) 297000 mmc; D-dimer 2.82 mg/L and lung consolidation with right pleural effusion (**Figure 1**).

**KEY WORDS**

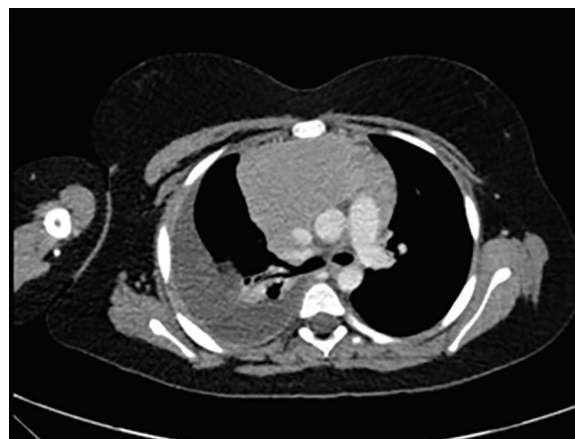
Case report; pleural effusion; bulky mass; differential diagnosis; children.



**Figure 1.** Approximately complete opacity of the right hemithorax as massive amount of pleural effusion.

The patient was therefore moved to our hospital for further study. At the time of admission, the child was eupneic. Although his condition was normal, the thoracic auscultation showed a respiratory silence in the right hemithorax. Moreover, laboratory tests confirmed the persistence of incremented phlogosis indexes (CRP 10.20 mg/Dl 21 x N, LDH 428 U/L, WBC 11780 mmc N50% L 45% PLT 288000 mmc); thus, an antibiotic therapy with amikacin and meropenem was started. The patient's past medical history was unremarkable. In consideration of his clinical presentation, we performed microbiological tests to exclude infectious diseases (serological tests for *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*; Quantiferon-TB Gold test for *Mycobacterium tuberculosis*). The exams came out negative, with absence of significant microbiological evidence supporting the radiological findings. His clinical conditions worsened within the first 24 hours. The patient became tachypneic, so oxygen support was required. After performing a thoracic ultrasound which showed the presence of massive pleural effusion in the right pleura with right lung atelectasis, a thoracentesis was performed, and 1000 cc of serum-haematic pleural fluid was drained and sent to laboratory for cytologic, microbiologic and microbacterium testing. The cytological analysis of pleural effusions showed cells compatible with T-lymphoma; accordingly, a chest computed tomography (CT) was performed, showing a voluminous "bulky" mass in the anterior mediastinum (**Figure 2**), so a neoplastic aetiology was suspected.

Finally, the bone marrow aspiration allowed us to diagnose T-cell acute lymphoblastic leukaemia (ALL). Hence, according to the International Protocol for Children and Adolescents With Acute Lymphoblastic Leukemia, chemotherapy was started and the patient's symptoms significantly improved as he responded well to the treatment.



**Figure 2.** A voluminous "bulky" mass in the anterior mediastinum, with hypodense structure, 9x7 cm. It coexists a copious right pleural effusion with passive atelectasia of the right lower lobe, part of medium and upper lobes. Moderate pericardic effusion.

## DISCUSSION

Infectious diseases, like pneumonia and pleuritis, can cause pleural effusion. It can be detected in 2% to 12% of children with community-acquired pneumonia (CAP) and up to 28% in case of hospitalization (3). In children with CAP, parapneumonic effusion may be suspected based on history and physical examination (4). Frequently, patients can be asymptomatic or refer to nonspecific symptoms like fever, malaise, loss of appetite, cough, dyspnea and chest pain, usually characterized by sudden and intense sharp, stabbing, or burning pain in the chest when inhaling and exhaling. The presence of prolonged fever, chest pain, and abdominal pain has been associated with parapneumonic effusion (4). Physical examination may show more specific clinical signs like dullness to percussion, decreased breath sounds, changes in the quality of breath sounds and transmitted speech over the effusion or respiratory silence to auscultation. Laboratory and radiologic findings, and also the appearance of the pleural effusion at drainage (**Table 1**), may help us to identify the underlying medical cause.

**Table 1.** Pleural fluid appearance and causes of PE.

Pleural fluid appearance	Causes of PE
Purulent fluid	Infection
Milky fluid	Chyle
Blood fluid	Trauma or malignancy

Chest radiography, including lateral decubitus views, should be used to confirm the presence of pleural fluid in children with CAP. If there is still a question of pleural fluid versus parenchymal opacification, thoracic ultrasounds (TUS) or CT scans are warranted. TUS are considered a safer imaging procedure than CT, owing to lack of ionizing radiation (4). Ultrasonography's (US) role in imaging the lung and extra cardiac mediastinum has evolved in the recent past. Although plain radiographs still remain the initial modality for paediatric chest imaging, there has been a significant increase in the clinical utility of thoracic ultrasounds in recent years. Ultrasounds are economical, easily available, portable and lack ionizing radiation. They can be performed after careful evaluation of the chest radiograph. Contrast administration and sedation are not required. The investigation can be performed at the bedside and allows real time visualization in various planes. In children presenting with breathlessness with or without fever where the chest radiograph reveals an opaque hemithorax, US helps in differentiating between pulmonary, pleural and mediastinal lesions and their morphological evaluation. Absence of air bronchograms on the chest radiograph is a clue to evaluating the child further with US (5).

TUS has recently become an extension of the physician's arm and has never been as important, both as a diagnostic tool, but also as a way to improve the safety of invasive procedures. It should be performed on every patient at their initial presentation and again whenever a pleural procedure is being performed. It will also provide information on the size and character of the effusion (6).

In fact, the role of US in confirming the presence of an effusion and differentiating it from pleural thickening is well established. The type of pleural effusion depends on the nature of the fluid collection. Serous fluid is usually a transudate and is a clear fluid or simple effusion. It may also be cloudy with or without swirling particles. An exudate or empyema is purulent fluid,

also classified as a complicated effusion. This shows multiple septa within and is multiloculated. Multiple septa in the fluid favours infections like tuberculosis. Long standing haemothorax will also show multiple thick septa within it, however the child will have a history of a decrease in haemoglobin and haematocrit levels. Quantification of the fluid and marking a site for diagnostic and therapeutic aspiration are well-established indications to perform an US. Movement of the fluid with change in posture confirms amenability of the fluid to aspiration. The multiloculated nature of pleural fluid may be better appreciable on an US than on a CT.

Ultrasounds are also useful in detecting lung or pleural masses masked by a large pleural effusion (5).

The management of parapneumonic effusions remains a disputed matter, and various therapeutic options are available. Supportive care measures, including appropriate oxygen therapy, fluid and electrolyte and nutrition management are important management steps not to be overlooked (7).

A conservative treatment with antibiotics alone is a reasonable option for small parapneumonic effusions, turning to the evacuation of effusions in case of an enlarging effusion (>2 cm), compromising respiratory function and/or associated with loculations.

It is advisable to start an intravenous antibiotic therapy with amoxi/clav with the possibility to add clindamycin in selected cases (e.g. complex patient or delay  $\geq 48$  hours before chest drain insertion or suspected loculated pneumonia) and, after 48 hours of treatment, in case of clinical stability or improvement, it is useful to continue the intravenous treatment until the child is afebrile for almost 48 hours and, at a later time is possible to switch methods of administration using the oral route. In our case we choose amikacin and meropenem to guarantee a wide action spectrum against the most common bacteria causing pneumonia and pleural effusion.

The optimal duration of antibiotic treatment for parapneumonic effusion or empyema is dependent on the adequacy of the drainage procedure and may vary by pathogen, but it has not been determined through randomized controlled trials. Treatment for 2-4 weeks is commonly recommended; some experts treat the infection for approximately 10 days after resolution

of fever (7). In case of no clinical improvement, it is suitable to perform a thoracic ultrasound or X-ray, and to discuss with the surgical team the possibility of practising chest drainage or to consider adding clindamycin.

However, sometimes, it is necessary to perform the drainage from the beginning, such as in case of complete unilateral whiteout with mediastinal shift, when respiratory support is required and in case of sepsis (4).

As we know, corticosteroids inhibit the expression of many proinflammatory cytokines and it has been postulated that they may be a useful adjunctive therapy in children with CAP. A recent study by Thimmesch M and colleagues (2) showed that corticosteroids could represent a noninvasive therapeutic option when antibiotics and pleural drainage have failed; nonetheless their use in children with complicated pneumonia is a topic of debate and current evidence does not support the routine use of systemic corticosteroids in children with CAP (7). Corticosteroid pretreatment is common among patients with high-risk disease features. While the indications for corticosteroid pretreatment are not confirmed, a higher disease burden at presentation and more symptoms can prompt a misdiagnosis and treatment intervention before a diagnosis of ALL is recognized, as it has been shown that high doses of steroids can have significant effects on immune responses.

Intrapleural fibrinolysis is usually suggested for effusions of thick fluid with loculations or empyema; and surgery is recommended in case of failure of treatment by antibiotics, chest tube drainage, and/or fibrinolytics (2).

According to the treatment established by A. Kapur *et al.* (8), chest drainage should be performed only in a small percentage of cases, considering clinical signs and the effusion size. Drainage of a parapneumonic effusion may be required for several reasons. If there is doubt about the infectious aetiology of the effusion or if malignancy is suspected, thoracentesis may be performed for cytologic examination. Finally, the size of the effusion and the degree of respiratory compromise are important factors to be considered when determining the management plan. Small effusions (<10 mm rim of fluid on lateral decubitus or less than one-

fourth of the hemithorax opacified on an upright chest radiograph) are likely to resolve on their own or often respond well to antibiotic therapy and usually require no further intervention. Moderate to large effusions are more likely to cause respiratory compromise, not resolve quickly, and benefit from drainage (4).

Thoracentesis (pleural aspiration) is a key intervention for both diagnostic and therapeutic purposes in the investigation and management of the patient with a unilateral pleural effusion. The use of thoracic ultrasound immediately prior to pleural intervention for suspected fluid has been strongly advocated for as a means of improving patient safety by reducing the frequency of iatrogenic complications and improving diagnostic yield (6).

In addition to infectious diseases, which are the most common causes of PE, also cardiovascular disease (e.g. congestive heart failure or constrictive pericarditis), lymphatic disorder (e.g. chylothorax or lymphangiectasia), intra-abdominal processes (e.g. pancreatitis or peritonitis), non-infectious lung diseases (e.g. pulmonary embolism or infarction) and cancer must be taken into account in the differential diagnosis of PE.

Particularly, pleural effusion may result from pleural invasion by the tumour, pneumonia, obstruction of lymphatic flow or atelectasis from an ab extrinsic compression.

Among the major malignant pathologies that can give rise to a pleural effusion there are lymphoma, leukaemia and carcinoma. Acute lymphoblastic leukaemia is a malignant proliferation of lymphoid cells blocked at an early stage of differentiation that can invade bone marrow, blood, and extramedullary sites (9).

It is the most common cancer in children and many studies demonstrate that it represents one of the most frequent causes of mediastinal mass, together with lymphoblastic leukaemia and Hodgkins lymphoma (10, 11).

The aetiology of ALL is unknown, but factors like ionizing radiation, infections, genetic factors, and chromosomal abnormalities play an essential role in the pathogenesis. ALL patients usually complain of symptoms reflecting bone marrow failure, including leucopenia, thrombocytopenia, and anemia, which present with bleeding, purpura, fatigue, malaise, and recurrent

infections. Although leukemia may manifest itself with extramedullary symptoms, it rarely causes malignant serous effusions, especially as the first manifestation (12). Pleural and pericardial effusions in patients with leukemia are more likely to be benign than malignant (13). Pleural effusion is a common finding in patients with Hodgkin and non-Hodgkin lymphomas, with a frequency of 20-30%, while leukemia rarely accompanies this manifestation (14).

In literature, pleural effusion in leukemia patients was often the result of underlying infections, secondary malignancy, or the toxicity of chemotherapy (14). Besides this, a study of 111 patients with acute leukemia or myelodysplastic syndrome who underwent pleural procedures showed the aetiology of the pleural effusion presented as infection for nearly half (47%), followed by malignant disease (36%), and volume overload (13%).

Kendre and colleagues reported a case of T-ALL that presented with pleuropericardial effusion, and according to the literature, this was more frequently documented with T-ALL (16, 17).

The pleural effusion will be bloody or chylous, and the cytopathologic study with a documented presence of malignant cells will be diagnostic.

In our case, the patient sustained massive pleural effusion, leading to the diagnosis of T-ALL. Clinical findings and symptoms could be similar to those previously mentioned, with the possible presence of unexplained weight loss and lymphadenopathy.

Patients with ALL may also develop symptoms related to the infiltration of blasts in the bone marrow, lymphoid system, and extramedullary sites (including the central nervous system [CNS] and testicles). These symptoms may include fatigue or lethargy, constitutional symptoms (eg, fevers, night sweats, weight loss), dyspnea, dizziness, infections, and easy bruising or bleeding. Chin numbness or facial palsy may result from cranial nerve or CNS involvement. Among children, pain in the extremities or joints may be the only presenting symptom. The presence of lymphadenopathy, splenomegaly, and/or hepatomegaly on physical examination may be found in approximately 20% of patients. Abdominal masses from gastrointestinal involvement are more suggestive of mature B-cell ALL (Burkitt lymphoma) (18).

The treatment of the underlying malignancy often leads to an improvement in the effusion.

The first-line treatment for acute lymphoblastic leukaemia typically includes four phases over 2-3 years: induction, consolidation, intensification, and long-term maintenance. In addition, directed treatment is given to prevent CNS relapse. Allogeneic haemopoietic cell transplantation is reserved for patients with high-risk disease or persistent minimal residual disease. This intensive therapeutic approach has led to an estimated 5-year overall survival of 90% of patients with childhood acute lymphoblastic leukaemia (19).

To our knowledge, there are no reported cases of T-ALL in children that initially presented with massive pleural effusion like those in our patient. This leads us to consider malignant serous effusion in leukemia uncommon, rarely as the first manifestation.

This case aims to emphasize the importance of considering rare causes of serous effusion as it may also mirror underlying leukaemia. In conclusion, a large and unilateral pleural effusion must always make us suspicious and lead to suspicion of on-haematologic disease. The earlier we can make a diagnosis; the earlier we can administer the appropriate treatment.

#### ACKNOWLEDGEMENTS

We would like to thank our patient, his parents, radiologists and thoracic surgeons for their collaboration.

#### COMPLIANCE WITH ETHICAL STANDARDS

The manuscript was written according to Good Clinical Practice.

#### Conflict of interests

The authors declare that they have no competing financial interests.

#### Financial support

The authors declare they have not received financial support.

#### Authorship

Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. All authors read and approved the final manuscript.

#### Author contributions

Wrote the manuscript: SC and MV; contributed to the discussion: FM, FF and SFR; collected the references:

GC and SAM; reviewed the manuscript: SM, LC and GZ. Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. All authors read and approved the final manuscript.

#### Ethical approval

##### Human studies and subjects

The manuscript was written according to Good Clinical Practice and compliance with the Declaration of Helsinki with successive amendments.

##### Animal studies

N/A.

##### Data sharing and data accessibility

The data underlying this article can be shared just before a reasonable request to the Corresponding Author.

##### Publication ethics

##### Plagiarism

All original studies are cited as appropriate.

##### Data falsification and fabrication

All the data correspond to the real.

##### Manipulation of images

All images are original.

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