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CASE REPORT

NECROTIZING PNEUMONIA IN CHILDREN: A CASE SERIES

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ABSTRACT: Necrotizing pneumoniae (NP) is a serious complication of community acquired pneumonia. Streptococcus pneumoniae is the most common cause of NP. Contrast-enhanced computerized tomography (CT) is more sensitive than plain radiographs for detecting suppurative complications of pneumoniae. NP requires a prolonged course of antimicrobial therapy, usually starting by the parental route. We present a case-series of 4 pediatric cases of NP, comparing the observed data with those described in the current literature. The clinical presentation and laboratory examinations were consistent with those reported in the literature. In most of our cases we made the diagnosis with contrast-enhanced computed tomography, however recent advances in magnetic resonance imaging sequences and protocols have made it a viable alternative for the diagnosis, as shown in 1 of our patients. As suggested by literature, the initial empiric therapy was broad-spectrum modified with a targeted therapy according to the antibiogram. There are only few studies that have evaluated long-term follow-up in patients who had NP. Lung function tests were initially altered in 2 out of 4 patients and chest x ray normalized in 6 months at maximum in all the 4 patients. 2 cases out of 4 underwent magnetic resonance imaging (MRI) after 10 months from the discharge. In both cases it showed persistent minimal residual signs of previous NP. We conclude that early diagnosis and adequate therapy are essential to prevent severe consequences and impairment of lung function. More studies are needed to define the follow-up, as early pneumonia could be a risk factor for impaired pulmonary function in adulthood.

ABBREVIATIONS

CAP: Community Acquired Pneumonia
CCAP: Complicated Community Acquired Pneumonia
CPAP: Continuous Positive Airway Pressure
CRP: C-Reactive Protein
CT: Computerized Tomography
ECG: Electrocardiogram
ED: Emergency Department
HFNC: High Flow Nasal Cannula
MM: Millimeters
MRI: Magnetic Resonance Imaging
MRSA: Methicillin Resistant Staphylococcus Aureus
NP: Necrotizing Pneumoniae

PICU: Pediatric Intensive Care Unit
TPR: Total Pulmonary Resistance
US: Ultrasound

KEY WORDS
Necrotizing pneumoniae; community acquired pneumonia; children; contrast-enhanced CT; complicated community acquired pneumonia.

Introduction

Necrotizing pneumoniae (NP) is a serious complication of community acquired pneumonia (CAP) which consists in destruction and necrosis of lung parenchyma and formation of cavities containing pus, necrotic material and air.(1). Although this complication rarely occurs in children, it may be associated with significant morbidity. A complicated CAP (CCAP) has to be suspected in all children with CAP who are not responding to conventional therapy.

Streptococcus pneumoniae (especially Serotype 3 and Serogroup 19) is the most common cause of necrotizing pneumoniae. Other frequent bacteria involved are methicillin resistant Staphylococcus aureus (MRSA), group A Streptococcus, Mycoplasma pneumoniae and Legionella. Another infectious cause of NP can be Aspergillus. (2–4) Rarely also Pseudomonas aeruginosa CAP evolves in NP(5).

Contrast-enhanced computed tomography (CT) is more sensitive than plain radiographs for detecting suppurative complications of pneumonia and it's helpful in differentiating necrotizing lesions from pulmonary abscesses, which require different management.

NP requires a prolonged course of antimicrobial therapy, usually starting by the parental route. If not adequately treated, necrotizing pneumoniae may lead to severe complications such as bronchopleural fistula, empyema, respiratory failure, and septic shock, especially in particular group of children with chronic conditions such as immunodeficiencies, malnutrition, chronic lung diseases, and cystic congenital thoracic malformations. (6)

We hereby present a case-series of 4 pediatric cases of necrotizing pneumoniae, highlighting the diagnostic algorithm. Three children were previously healthy, while one of them was diagnosed with Down Syndrome.

Case 1

A previously healthy 8-year-old male from Italy presented at the emergency department (ED) complaining of fever, cough and right-chest pain for five days. At first clinical evaluation the patient was well appearing, eupneic, with no signs of respiratory distress. Auscultation of his chest didn't reveal pathological sounds. Blood exams and blood culture were performed. Laboratory values of significance included a slight neutrophilic leukocytosis (total white blood cell count of 14,920/mmc with 63.1% of neutrophils) with increase in c-reactive protein (CRP) levels (105.9 mg/L with normal values below 10 mg/L). Venous blood gas electrolytes and basic blood chemistry were normal.

Electrocardiogram (ECG) was unremarkable. A chest x-ray showed right subclavicular pulmonary thickening with suspected air-fluid level (***Fig. 1***). Contrast-enhanced chest CT revealed rounded focal lesion of the right upper lobe of about 35 millimeters (mm) in diameter characterized by a necrotic central component and by a thin border of consolidated lung, as in necrotizing pneumonia, with millimetric gaseous components in the context; modest "glass" consolidation alterations of the adjacent parenchyma and thickening of the interlobular septa; minimum thickening of the lesser fissure and superior blade of the greater fissure and multiple reactive lymph nodes (***Fig. 2***).

Given the clinical history and the CT findings, the patient was admitted to our inpatient unit. Microbiological investigations such as blood culture, sputum culture and nasopharyngeal aspirate were performed and intravenous antibiotic therapy with ampicillin sulbactam was initiated. Tuberculin skin test and quantiferon were negative.
A pansusceptible Streptococcus pneumoniae was isolated from the sputum culture, while the blood culture showed a negative result. On the fourth day of hospitalization given the persistence of fever with elevated level of CRP, the antibiotic therapy was modified with clindamycin and piperacillin tazobactam, in order to have better synergisitic acitivity towards MRSA, gram negative and anaerobic bacteria.
Thereafter, a good clinical and laboratory response were observed. The antibiotic therapy was continued intravenously for 14 days. A chest x-ray before discharge showed reduction of the thickening in the right upper field. After 18 days of hospitalization the patient was discharged.

Clinical and imaging follow-up

After 1 month from the discharge the patient still complained reduced tolerance to exercise. At 6 months exercise symptoms resolved. Respiratory function tests with plethysmographic technique performed after 1 month from the discharge revealed a moderate increase in total pulmonary resistance (TPR), which was 338% of predicted value (PV). At the check-up after 5 months from the discharge, the situation improved with a drop in TPR (183% of PV).
A chest x-ray performed 1 month after the discharge was normal. ***(Fig. 3)***. A chest magnetic resonance imaging (MRI) performed after 6 months from the hospitalization detected a minimal peribronchial inflammatory component in the area of the previous pneumonia (***Fig. 4***).

Case 2

A 20 month old male was referred to our hospital for fever and cough for 3 days, worsening with increasing dyspnea and low food intake.
The patient was affected by Down Syndrome (without associated comorbidities).
Upon arrival at our ED, the patient was pale, tachypneic (respiratory rate 60/70 per minute), his oxygen saturation was 92% in room air, heart rate 180 beats/min and his auricular temperature (AT) was 39.6°C. Auscultation revealed a reduced vesicular murmur in the left pulmonary field and crackles in the basal fields.
A chest x-ray showed extensive parenchymal consolidation at the left basal and middle fields, associated with pleural effusion extended from the base to the apex, with maximum thickness in the lower mantle of about 2 cm ***(Fig. 5)***.
A complete blood cell count showed a neutrophilic leukocytosis (WBC 21.940/mmc with 86.6% of neutrophils) with increase in CRP levels (265.2 mg/L). Venous blood gas electrolytes and basic blood chemistry were normal. High flow oxygen therapy (HFNC) with initial FiO2 of 0.5 was started and, after performing microbiological exams (blood culture, nasal swab, urinary antigens for Legionella and S. pneumoniae), empiric intravenous antibiotic therapy with ceftriaxone was started.
Considering the persistent impaired breathing mechanics, with oxygen desaturation despite the maximal HFNC therapy, the patient was admitted to the Pediatric Intensive Care Unit (PICU), where continuous positive airway pressure (CPAP) therapy was started with a positive end expiratory pressure (PEEP) of 8 mmHg and inspiratory fraction of oxygen (FiO2) of 50%.
CPAP therapy was continued for 2 days with progressive decreasing requirement of positive end expiratory pressure (PEEP) and inspiratory fraction of oxygen (FiO2). Ventilatory therapy was then modified in HFNC therapy, which was continued for 7 days.
On the 3rd day of hospitalization, a chest radiograph showed *left mid-basal* p*neumatoceles (the largest one of 3 cm in diameter), with unchanged pleural effusion.* A contrast-enhanced CT of the chest showed *l*eft pleural effusion with maximal thickness of 27 mm, apical-posterior pocket air layer,

consolidation in the left lower lobe with areas of colliquative appearance and confluent air cavities, atelectatic consolidation in the left upper lobe, slight shift of the chest towards the right of the midline, suggesting necrotizing pneumonia with bronchopleural fistula and empyema (***Fig. 6-7***). A surgical consultation was required, a thoracic drainage was then placed, with outflow of serum-blood material. The drainage was definitively removed after 6 days due to a clear reduction in the effusion at lung ultrasound (US).

Candida parapsilosis was isolated by bronchoalveolar lavage, interpreted as contamination from oropharyngeal colonization. The culture of pleural fluid showed a negative result. Streptococcus pneumoniae was isolated from both blood and urine cultures, and positive viral PCR for rhinovirus resulted from a nasal swab.

Considering the persistence of febrile peaks on the 4th day of hospitalization, the antibiotic therapy was modified and intravenous vancomycin was added to the third-generation cephalosporin, with a a good clinical and laboratory response: the fever decreased to stable apyrexia from the 10th day of hospitalization, and from the 11th day the patient was oxygen-independent.

In view of the stable conditions of the patient on the 10th day he was transferred from PICU to our inpatient pediatric unit. The antibiotic therapy with vancomycin was continued intravenously for a total of 10 days and cefotaxime was continued for 14 days. Serial lung US were performed showing a progressive reduction in the extension of the pleural effusion. The last US performed before discharge showed left pleural thickening without evident pleural effusion and the known inhomogeneous parenchymal consolidation with a hypo-aneocogenic area (about 4.5 cm in maximum diameter) with contextual hydro-aerial level.

After discussion of the case with the pulmonologist, it was decided to continue the intravenous antibiotic therapy. Patient's family expressed the willingness to self-discharge from the hospital. The patient was then discharged, with indications to continue oral antibiotic therapy with cefpodoxime 10 mg/kg/die and with an outpatient appointment one week later to repeat a lung US. This patient was lost to follow-up.

Case 3

A previously healthy Italian 3-year-old boy presented at ED complaining for 10 days asthenia and dyspnea on exertion. He also had fever for 5 days associated with wet cough. 3 days earlier he was evaluated at another ED, where he was discharged with the diagnosis of pharyngitis and indication to start antibiotic therapy with amoxicillin-clavulanate at a dosage of 80 mg/kg/day in 3 daily doses. Due to the persistence of the fever and the symptoms together with reduced food intake, he was therefore taken to our ED. At admission, the patient was well appearing, feverish (AT 38.1°C), heart rate 164 beats/min and oxygen saturation 94% in room air. His respiratory examination was significant for reduced vesicular murmur in the middle and basal lung fields. The remainder of his clinical examination was normal. Laboratory values of significance included a slight increase in total WBC (17,030/mmc) with 72% of neutrophils, an increase in inflammatory index (CPR 44.4 mg/l) and slight increase in transaminase levels (AST and ALT 69 U/L, with normal values up to 34 and 49 respectively). Venous blood gas was normal (pH 7.4, pCO2 40 mmHg, HCO3- 25 mmol/l, lac 1.7 mmol/l).

A chest x-ray showed a *left basal retro-paracardial parenchymal consolidation with flap of pleural effusion and hilar enlargement and elevation of the left hemidiaphragm (**Fig. 8**).*

The patient was then admitted to the pediatric department for further evaluation and management.

Intravenous ceftriaxone (80 mg/kg/die) and oral clarithromycin (15 mg/kg/die) were started.

On the fifth day of hospitalization, due to the persistence of fever and the persistent need of oxygen-supplementation, a chest x-ray was performed showing *two rounded hyper diaphanous images in the lower left perihilar site of 1 and 2 cm in diameter respectively, with signs consistent for cavitation, and the apical-basal pleural effusion layer on the left which was unchanged (**Fig 9**).*

A pulmonologist consultation was then performed, which indicated the switching from intravenous ceftriaxone to intravenous piperacillin-tazobactam (300 mg/kg/die). A blood culture was performed before the switch which resulted negative.
After six days of hospitalization a chest CT found a *left mid-baseline necrotizing pneumonia (see **Fig. 10- 11**).* Intravenous vancomycin (40 mg/kg/die in 4 doses/die) was added to the current therapy to cover MRSA. Subsequently there was a good clinical response and serial lung US revealed the reduction and resolution of the left pleural effusion. The antibiotic therapy with piperacillin-tazobactam and vancomycin was continued for 24 and 21 days, respectively. The patient required 1 month of hospitalization.
As a side effect of antibiotic therapy, blood tests performed during therapy showed progressive leukopenia and neutropenia (at nadir WBC were 2,100/mmc and neutrophils 190/mmc). Two doses of subcutaneous granulokines were administered, with excellent laboratory response (WBC 19,920/mmc, 12,550 neutrophils/mmc). Moreover, during the third week of hospitalization the patient had intercurrent febrile gastroenteritis. The microbiological tests performed (blood cultures, coproculture, PCR for gastroenteric bacteria, search for fecal viral antigens) showed positive findings on the stool for Norovirus (antigen) and for Clostridium difficile (antigen and PCR). Therefore, antibiotic therapy with metronidazole was added to current therapy for 10 days.

Clinical and imaging follow-up

The patient didn't complain any symptoms from the discharge. A spirometry was performed after 8 months showed an obstructive pattern (FEF 25-75% before bronchodilator test was 46% of the predicted value, while after bronchodilator test 100% of the predicted value; FVC 84% of the predicted value). Consequently, the patient was given a bronchodilator therapy with salbutamol for few days, followed by fluticasone spray for 2 weeks. A second spirometry was performed 10 months from the discharge and it showed a normal pattern (FEF 25-75% was100% of the predicted value, FVC 91% of the predicted value).
At 3 weeks from the hospital discharge lung US revealed "*improvement with further reduction (currently 2 mm) of consolidation in the upper left lung field in the posterior area, also reduction of multiple B lines, no pleural effusion*". But at 3 months lung US showed "*a mild pleural irregularity in the left posterosuperior area of the lung with minimal accentuation of the B lines, without any consolidation in the parenchyma neither pleural effusion*". At 7 months chest x-ray found "*reduction of diaphany in the left retrocardiac site, in the site of the previous alteration, without signs of pleural effusion*" (***Fig. 12***). After 10 months chest MRI showed "*a minimal thickening of the pleura in the left posterior parietal area with associated thin fibrotic striae, without consolidations of the parenchyma*" (***Fig. 13***).

Case 4

A previously healthy 11-year-old boy was referred to a local ED for left hemithorax pain since one week associated with intermittent fever and productive wet cough over the past two days. His ear temperature was 36.5°C, heart rate 95 beats/min and oxygen saturation 94% in room air. Respiratory examination showed reduced vesicular murmur on the left side and no sound on the left pulmonary basis. Blood analysis showed neutrophilic leukocytosis (WBC 24,220/mmc of which neutrophils 86%) and increased CRP levels (57 mg/L, about five times over normal values). A chest x-ray *showed pleural effusion in the left hemithorax with lower perihilar parenchymal thickening (**Fig. 14**).*
The patient was then admitted to the pediatric department, where intravenous antibiotic therapy with piperacillin-tazobactam was started together with intravenous methylprednisolone. Clinical conditions of the patient gradually improved. Microbiological tests showed positive IgG and IgA values of Chlamydia pneumoniae. On this basis, on the 5th day of hospitalization oral clarithromycin

was added to the current therapy. A chest CT scan found *an 18 mm pleural effusion at the base of the left lung, with thickening of the adjacent parenchymal tissue.*
After eleven days of hospitalization the patient was discharged with pneumological follow-up. Oral clarithromycin and amoxicillin with clavulanic acid was continued at home to complete two weeks of antibiotic therapy; oral deltacortene was also required at home with slowly decreasing doses for one week after hospital discharge.
Two weeks after hospital discharge the patient presented at our ED complaining again of left hemithorax pain and fever. At admission, the patient was well appearing, AT 38.3°C, heart rate 138 beats/min, oxygen saturation 97% in room air. His respiratory examination was significant for reduced vesicular murmur and presence of crackles in the left middle and basal lung fields. Blood analysis showed neutrophilic leukocytosis (WBC 15,490/mmc of which neutrophils 70%) and increase in the CRP levels (147.5 mg/L). A chest x-ray showed *extensive radiopacity at the base of the left hemithorax with partly defined and partly irregular profiles, with pleural connection and contextual apparent hydro-aircraft level of approximately 1.5 cm. An area of rounded hyperdiaphany at the lateral left basis and a mantle radiopacity from the base to the upper third of the left hemithorax coexisted, suggestive for pleural effusion and thickening.*
An empiric intravenous antibiotic treatment with piperacillina-tazobactam and vancomycin was started, after performing blood culture, at the admission at our Pediatric department. A chest MRI showed, in the left lower lobe, *a consolidative area of 6.5 x 2.5 x 4 cm with contrast enhancement of the profiles and large central cavitated area (7 cm) with a predominantly fluid component and with air bubbles, suggestive for phlogistic thickening evolving in abscess. A thickening and contrast enhancement of the surrounding pleura was also reported* ***(Fig. 15***).
The blood culture resulted negative, Chlamydia pneumonia recent infection was confirmed (IgG and IgA levels were respectively 3 times and 8 times above the values considered negatives) The PCR test for the most common respiratory viruses on a nasal swab was negative.
The antibiotic treatment with piperacillin-tazobactam and vancomycin was continued for 4 and 3 weeks, respectively.
During hospitalization, serial lung US examinations were performed, showing progressive reduction in the size of the consolidation (2.3 cm after 4 weeks of treatment), with persistence of thickening and non-homogeneity of the adjacent parietal pleura. Immunological analysis (immunoglobulins IgM, IgA and IgG, lymphocyte subpopulations) were normal and HIV serology was negative.
To optimize the respiratory function of the patient, the pediatric pneumologist prescribed respiratory physiotherapy with PEP mask (started with resistance of 7-8 cmH2O and subsequently reduced to 2.5 cmH2O).
Serial blood analysis documented the decreasing of CRP levels and normalization of the blood count. After 1 month of hospitalization the patient was discharged. At home he continued oral antibiotic treatment with cefpodoxime for 10 days.

Clinical and imaging follow-up

The patient continued to complain of mild and decreasing chest pain for two weeks after the discharge. Spirometry with plethysmographic technique at 1, 3 and 6 months showed mild increase in total pulmonary resistance (which were respectively 302%, 234% and 352% of the predicted value) and reduction in vital capacity, which normalized after 6 months from the discharge (vital capacity at 1, 3, 6 months was respectively 67%, 79% and 80% of the predicted value). Respiratory physiotherapy with PEP mask was continued for 6 months and azithromycin prophylaxis was prescribed for 6 months (3 days/week).
Lung US performed at 2 weeks, 1 month and 3 months from the hospital discharge showed progressive reduction of the consolidation and pleural thickening. A chest x-ray performed 6 months after the discharge was normal.

Discussion

NP is a serious complication of CAP which has to be suspected in all children who are not responsive to firstline therapy. Unfortunately, NP can afflict a broad spectrum of ages, as our patients ranged from 1.5 yo to 11 yo consistent with what has been reported in literature. (7)

According to literature data, (8) NP incidence shows seasonal preference for fall and winter (8).

The clinical presentation of NP consists of fever, respiratory signs and symptoms and radiographic signs of a non-responding pneumonia, (7) as our patients showed.

Increased WBC (≥ 15,100/mmc) and elevated CRP (≥ 121.5 mg/L) have been reported as highly predictive of NP,(9) consistently with our patients who had increased inflammatory markers.

Even if US or chest x-ray may support the diagnosis, contrast-enhanced CT is considered the most sensitive technique to detect further complications of pneumonia. A recent study by Carrard et al. (10) have retrospectively compared the effectiveness of ultrasound vs. CT in diagnosing NP in 41 patients with median age of 46 months (range 17-182 months), concluding that ultrasound is very useful in the presence of pleural effusions because of the better acoustic window provided by the fluid. Furthermore, ultrasound is superior to CT in visualizing septations within pleural effusions and therefore it is useful particularly when the placement of a pleural drain may be needed. Furthermore, recent advances in MRI sequences and protocols have made MRI a viable alternative for the diagnosis of CAP and its complications, particularly in centers with appropriate expertise and resources.(11) In our report chest x-ray and the US performed in the ED raised the suspicion of CCAP in 2 cases out of 4; in the remaining cases the absence of clinical response to antibiotic therapy was suggestive for a CCAP. In 3 cases out of 4 the diagnosis was confirmed by chest CT, as described in similar case reports. In case 4 the patient had a recent history of CAP with pleural effusion and the diagnosis of NP was made on the basis of a chest MRI, as the patient had had a recent CT scan during the previous hospitalization (7).

Even if pneumonia with or without complications is uncommonly associated with bacteremia (6), it is important to perform blood culture and, if possible, sputum culture. Urinary antigens for Streptococcus pneumoniae have a high rate of false positives (being responsible of asymptomatic nasal colonization in humans) but might be useful in the presence of respiratory symptoms. The Paediatric Infectious Diseases Society and the Infectious Disease Society of America recommends a bronchoalveolar lavage for patients with CCAP without a microbiological diagnosis on initial testing, or for those who are not responding to treatment.(12)

In our case series microbiological findings detected Streptococcus pneumoniae in 50% of patients. Streptococcus pneumoniae Serotype 3 has been reported to be the most common cause of NP before pneumococcal conjugate vaccine 13 (PVC13) was introduced, but it is still the most frequent etiologic agent in post-PCV period (13). This finding may be explained as PCV13 efficacy against Serotype 3 is modest, probably because intrinsic properties (such as thicker polysaccharide capsule) require higher levels of antibody concentration to prevent pneumonia complications (13-14).

NP requires prolonged antibiotic treatment. The initial empiric therapy must be broad-spectrum, taking into consideration local patterns of antibiotic resistance and whether the child has any underlying comorbidities (6). The antibiotic treatment might be subsequently modified with a targeted therapy according to the antibiogram and considering the clinical response.

In case 1, 2 and 4 the poor clinical response to the current therapy led us to modify it in order to have better efficacy against MRSA and Pseudomonas aeruginosa. In case 3 the blood culture was performed after the beginning of antibiotic therapy and showed a negative result, therefore broad-spectrum antibiotic therapy was performed for the entire duration of the treatment.

Bronchoalveolar lavage was not performed because in our clinical practice it is limited to cases that are poorly responsive to broad-spectrum antibiotical therapy.

The duration of antibiotic therapy is still debated; it is suggested a range between 2-3 weeks in total (6). The transition to oral antibiotic therapy should be made as soon as possible according to the improvement of symptoms and signs of infection and based on the child's ability to take the therapy.(15–17) Our patients were treated differently because there is still no hospital protocol for the treatment of NP and in our cases treatment was determined by the patients' clinical course and microbiological tests.

The treatment must be immediate and adequate, to reduce the risk of further complications of NP. In our study only 1 out of 4 patients (25%) developed bronchopleural fistula and empyema as complications. In literature NP has been reported to be associated more frequently with bronchopleural fistula (17–67%) (7, 8), empyema (63-100%), (7,8) similarly to our case series. Other complications include acute respiratory distress syndrome, (18) septic shock, (19) especially in children with risk factors (immunodeficiencies, malnutrition, chronic lung diseases, congenital cystic lung disease). ~~A~~ Recently Carloni et al. conducted a retrospective study on 43 children with diagnosis of NP between 2005 and 2019. The median age was 44 months (range 32-62 months), most were previously healthy (93%) and no one had any known risk factors for NP. In 32 children NP was associated with empyema, in 2 with bronchopleural fistula and in 2 with atypical hemolytic uremic syndrome (13). Increased awareness and early detection of complications are essential to reduce long-term sequelae and to reduce mortality.

Surgical treatments of pediatric NP are recommended in case of complications or no complete response to the pharmacological treatment (7, 20). In fact, in our report pediatric surgeons placed a thoracic drainage only in the patient who developed empyema. Lung resection in children is rare, as it may reduce future pulmonary function (21).

While for patients with uncomplicated CAP, the indication for starting any medium-long term follow-up depends on the clinic and is not routinely recommended; the patients with CCAP must be monitored with clinical-radiological evaluations and pulmonary function tests, considering the risk of sequelae. Recently, Allinsons et. published a longitudinal observational study conducted in Great Britain. The study was made collecting data of a cohort of all single births among married women during 1 week in March 1946. All the participants were contacted 25 times between birth and age 73 years (2733 patients out of 5362 completed the follow up). The study showed that among the respiratory-cause deaths between age 26 and 73 years, 1/5 presented a low tract respiratory infection before the age of 2 years. This association remained strong also correcting the data for childhood socioeconomic position, home cohabitants, sex, birthweight and adult smoking. These findings are consistent with an increased rate of early adult deaths from respiratory disease in subjects who had low respiratory tract infections in the first 2 years of life (22). These findings support the need for NP follow-up which, at the moment, is mostly based on expert opinion rather than evidence-based indications.(6)

For the radiological follow-up MRI is a radiation-free technique providing an excellent resolution for soft-tissue and for anatomical details. Even if it is known that MRI can be an appropriate follow-up technique to identify residual abnormalities, there are no studies reporting long-term radiological data on MRI in patients with NP. There are few studies reporting long-term radiological data based on CT scan or chest x-ray. In the study of Donnelly et al. most of patients who underwent a long-term follow-up showed an almost complete normalization of the pulmonary parenchyma in 3-8 months, only three patients with history of parapneumonic effusion showed a residual pleural thickening without pulmonary abnormalities.(23) In the retrospective study of Congeni et al. follow-up CT scans performed between 6 months and 10 years later were normal.(24) Sawicki et al. used a 6 months follow-up protocol with chest x-ray and/or CT scan, showing a marked improvement of the lesions with near normalization of the lung parenchyma.(2) Iglesias et al. conducted a retrospective-prospective observational study in children with NP admitted to PICU, most of the patients underwent a long-term follow-up with chest x-ray, with a median time to normalization of 3 months.(3) All our

patients underwent clinical and radiological follow-up using chest x-ray, lung US and MRI after hospitalization. All our patients had a progressively improving clinical course and they were clinically recovered at time of discharge. This was probably due to the rapid initiation of appropriate broad-spectrum antibiotic therapy and, in the third case, also to the placement of a chest drain.
Lung function tests in patient 1 and 4 initially showed increased pulmonary resistances which normalized 6 months after discharge. Patient 3 had normal spirometry after 10 months from the discharge.
Chest x-ray showed no signs of previous NP in case 1 after 1 month from the discharge, whereas in cases 3 and 4 after 6-7 months from the discharge. 2 cases out of 4 underwent MRI after 10 months from the discharge. In both cases it showed persistent minimal residual signs of previous NP.
There are only few studies that have evaluated long-term lung function in patients who had NP. In Sawicki et al. report, 12 patients underwent follow-up with pulmonary function at 6 months after diagnosis of NP: 8 patients had normal function, 3 had mild obstructive pattern and 1 mild restrictive pattern (2). A recent Spanish study reported normal spirometry with no evidence of obstructive pulmonary disease or restrictive patterns 8 years after the first episode of NP, except in one patient with a FVC in the lower limit of normal (25).

As suggested by few studies, early pneumonia could be a risk factor for impaired pulmonary function in adulthood (like asthma and chronic obstructive pulmonary disease) (2, 26). Data on Long-term lung function is lacking. Hence, monitoring lung function over time is warranted to better study sequelae of NP in adulthood.

Conclusions

NP represent a severe complication of CAP in children. Early diagnosis and adequate therapy are essential to prevent severe consequences and impairment of lung function. Pulmonary function should be evaluated in long-term monitoring even in adulthood, even if long-term follow-up guidelines are still needed.

References

1. Tsai YF, Ku YH. Necrotizing pneumonia: a rare complication of pneumonia requiring special consideration. Curr OpinPulm Med. 2012 May;18(3):246–52.
2. Sawicki GS, Lu FL, Valim C, Cleveland RH, Colin AA. Necrotising pneumonia is an increasingly detected complication of pneumonia in children. European Respiratory Journal. 2008;31(6):1285–91.
3. Blanco-Iglesias E, Oñoro G, Almodovar-Martín JL, García-Salido A, De Lama Caro-Patón G, Martínez de Azagra-Garde A, et al. Retrospective Study in Children With Necrotizing Pneumonia: Nine Years of Intensive Care Experience. Pediatr Infect Dis J. 2020 Jul;39(7):571–5.
4. Ness-Cochinwala M, Kobaitri K, Totapally BR. Characteristics and Outcomes of Children With Necrotizing Pneumonia. Pediatr Crit Care Med. 2021 Dec;22(12):e640–3.
5. Maharaj S, Isache C, Seegobin K, Chang S, Nelson G. Necrotizing Pseudomonas aeruginosa Community-Acquired Pneumonia: A Case Report and Review of the Literature . Case Rep Infect Dis. 2017;2017:1–5.
6. De Benedictis FM, Kerem E, Chang AB, Colin AA, Zar HJ, Bush A. Complicated pneumonia in children. The Lancet [Internet]. 2020;396(10253):786–98.
7. Masters IB, Isles AF, Grimwood K. Necrotizing pneumonia: an emerging problem in children? Pneumonia. 2017;9(1):1–19.
8. Krenke K, Sanocki M, Urbankowska E, Kraj G, Krawiec M, Urbankowski T, et al. Necrotizing pneumonia and its complications in children. Adv Exp Med Biol. 2015;857(June 2016):9–17.

9. Liu SS, Song LJ, Meng FZ, Peng L, Liu YH. Early predictors of necrotizing pneumonia in children. Chinese Journal of Contemporary Pediatrics. 2016;18(5):391–5.
10. Carrard J, Bacher S, Rochat-Guignard I, Knebel JF, Alamo L, Meuwly JY, et al. Necrotizing pneumonia in children: Chest computed tomography vs. lung ultrasound. Front Pediatr. 2022;10.
11. Alexopoulou E, Prountzos S, Raissaki M, Mazioti A, Caro-Dominguez P, Hirsch FW, et al. Imaging of Acute Complications of Community-Acquired Pneumonia in the Paediatric Population—From Chest Radiography to MRI. Children. 2024;11(1).
12. Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: Clinical practice guidelines by the pediatric infectious diseases society and the infectious diseases society of America. Clinical Infectious Diseases. 2011;53(7):25–76.
13. Carloni I, Ricci S, Rubino C, Cobellis G, Rinaldelli G, Azzari C, et al. Necrotizing pneumonia among Italian children in the pneumococcal conjugate vaccine era. PediatrPulmonol. 2021;56(5):1127–35.
14. McKee AJ, Ives A, Balfour-Lynn IM. Increased incidence of bronchopulmonary fistulas complicating pediatric pneumonia. PediatrPulmonol. 2011;46(7):717–21.
15. Atkinson M, Lakhanpaul M, Smyth A, Vyas H, Weston V, Sithole J, et al. Comparison of oral amoxicillin and intravenous benzyl penicillin for community acquired pneumonia in children (PIVOT trial): A multicentre pragmatic randomised controlled equivalence trial. Thorax. 2007;62(12):1102–6.
16. Addo-Yobo E, Chisaka N, Hassan M, Hibberd P, Lozano JM, Jeena P, et al. Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: A randomisedmulticentre equivalency study. Lancet. 2004;364(9440):1141–8.
17. Agweyu A, Gathara D, Oliwa J, Muinga N, Edwards T, Allen E, et al. Oral amoxicillin versus benzyl penicillin for severe pneumonia among Kenyan children: A pragmatic randomized controlled noninferiority trial. Clinical Infectious Diseases. 2015;60(8):1216–24.
18. Stroud MH, Okhuysen-Cawley R, Jaquiss R, Berlinski A, Fiser RT. Successful use of extracorporeal membrane oxygenation in severe necrotizing pneumonia caused by Staphylococcus aureus. Pediatric Critical Care Medicine. 2007;8(3):282–7.
19. Schwartz KL, Nourse C. Panton-Valentine leukocidin-associated Staphylococcus aureus necrotizing pneumonia in infants: A report of four cases and review of the literature. Eur J Pediatr. 2012;171(4):711–7.
20. Chen Y, Li L, Wang C, Zhang Y, Zhou Y. Necrotizing Pneumonia in Children: Early Recognition and Management. J Clin Med. 2023;12(6).
21. Ayed AK, Al-Rowayeh A. Lung resection in children for infectious pulmonary diseases. Pediatr Surg Int. 2005;21(8):604–8.
22. Allinson JP, Chaturvedi N, Wong A, Shah I, Donaldson GC, Wedzicha JA, et al. Early childhood lower respiratory tract infection and premature adult death from respiratory disease in Great Britain: a national birth cohort study. The Lancet [Internet]. 2023;401(10383):1183–93. Available from: http://dx.doi.org/10.1016/S0140-6736(23)00131-9
23. Donnelly LF, Klosterman LA. Cavitary necrosis complicating pneumonia in children: Sequential findings on chest radiography. American Journal of Roentgenology. 1998;171(1):253–6.
24. Congeni BL, Gaisie G. Clinical Course and Long Term Outcomes in Pediatric Patients with Necrotizing Pneumonia (NP). Pediatr Res [Internet]. 1999;45(7):159. Available from: https://doi.org/10.1203/00006450-199904020-00943
25. Bover-Bauza C, Osona B, Gil JA, Peña-Zarza JA, Figuerola J. Long-term outcomes of necrotizing pneumonia. Anales de Pediatría (English Edition). 2021;95(5):298–306.

26. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. Combined Impact of Smoking and Early-Life Exposures on Adult Lung Function Trajectories. Am J Respir Crit Care Med. 2017;196(8):1021-1030.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authorship
We observed the credit criteria.

Author contributions
The authors confirm contribution to the paper as follows. Paper conception and design BC, RS, GM, CF and DE; data collection BC, RS and CF; data interpretation FA, MM, ZS, MA, FL, BC, RS and CF; draft manuscript preparation BC, RS and CF; critical revision ZGV, DE and GM; supervision. All authors reviewed the paper and approved the final version of the manuscript.

Ethical approval
N/A

Informed consent
Informed consent from patient's parents was obtained to publish the cases and its images.

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FIGURES' CAPTIONS
Figure 1. Chest X-ray taken in the emergency room, showing parenchymal thickening in the right upper field.
Figure 2. Chest CT (transverse section) showing 35 mm thickening in the right upper lobe, with central necrosis and millimeter gas-containing areas.
Figure 3. Chest X-ray performed 1 month after discharge at which pulmonary consolidation is no longer evident.
Figure 4. Thoracic MRI (transverse section) that shows residual peribronchial inflammation in the area of the previous consolidation.
Figure 5. Chest x-ray performed in the ED department showing extensive parenchymal consolidation at the left basal and middle fields, associated with pleural effusion extended from the base to the apex, with maximum thickness in the lower mantle of about 2 cm.
Figure 6 and 7. Contrast-enhanced CT (transverse sections) showing copious left pleural effusion with maximal thickness of 27 mm, apical-posterior pocket air layer, consolidation in the left lower lobe with areas of colliquative appearance and confluent air cavities, atelectatic consolidation in the left upper lobe, slight shift of the chest towards the right of the midline.

Figure 8 and 9. Chest x-ray performed in the ED department showing respectively: a left basal retro-paracardial parenchymal consolidation with flap of pleural effusion and hilar enlargement and elevation of the left hemidiaphragm; two rounded hyperdiaphanous images in the lower left perihilar site of 1 and 2 cm in diameter respectively, with signs consistent for cavitation, with unchanged apical-basal pleural effusion layer on the left.

Figure 10 and 11. Contrast-enhanced CT showing left mid-baseline necrotizing pneumonia.

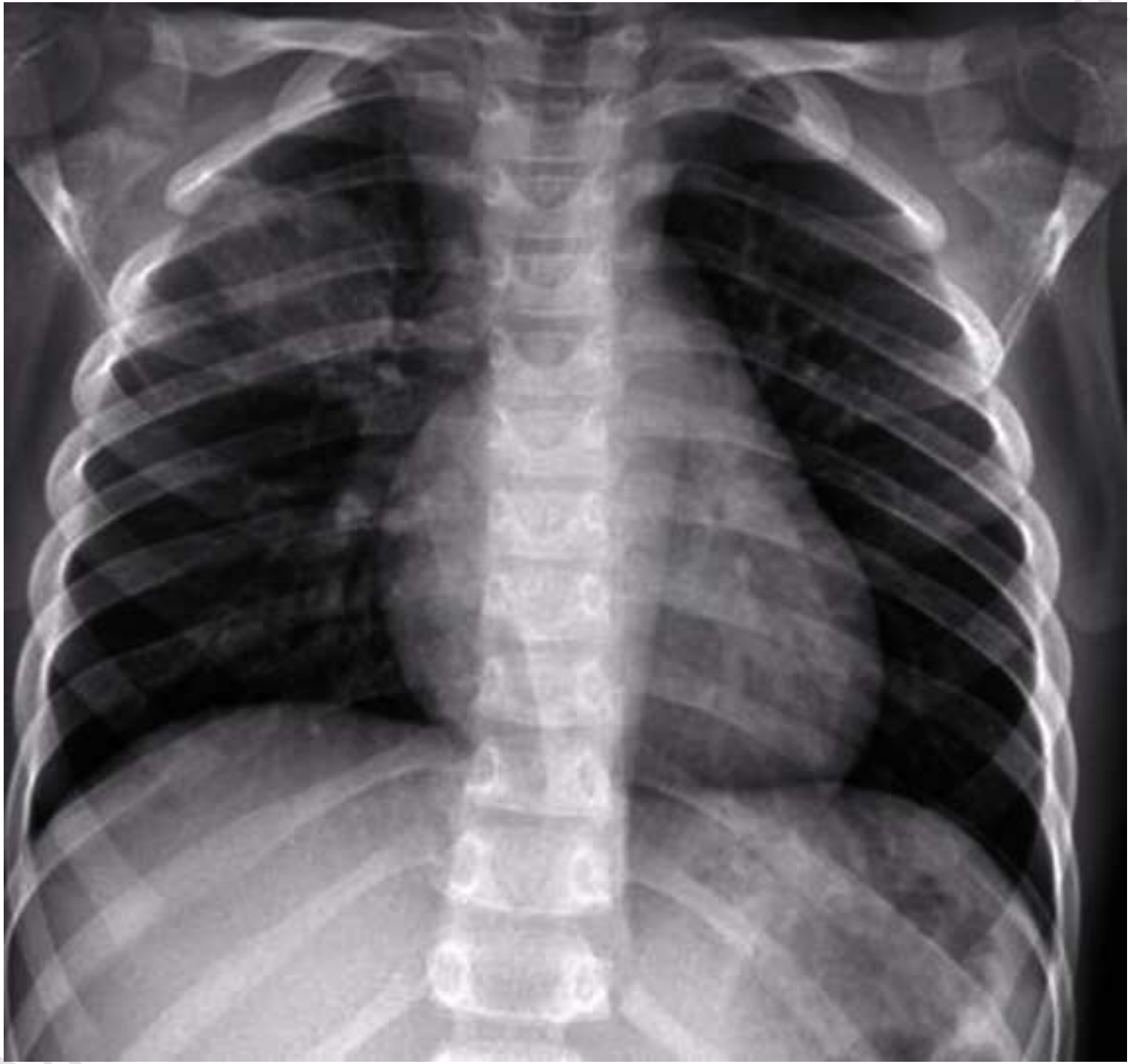
Figure 12. Chest x-ray performed after 7 months from the hospital discharge showing reduction of diaphany in the left retrocardiac site without signs of pleural effusion

Figure 13. Chest MRI performed after 10 months from the hospital discharge showing a minimal thickening of the pleura in the left posterior parietal area with associated thin fibrotic striae.

Figure 14. Chest x-ray performed at the ED showing pleural effusion in the left hemithorax with lower perihilar parenchymal thickening.

Figure 15. Chest MRI (transverse sections) showing a consolidative area of 6,5 x 2,5 x 4 cm with contrast enhancement of the profiles and large central cavitated area (7 cm) with a predominantly fluid component and with air bubbles, suggestive for phlogistic thickening evolving in abscess. A thickening and contrast enhancement of the surrounding pleura was also reported.

Figure 1



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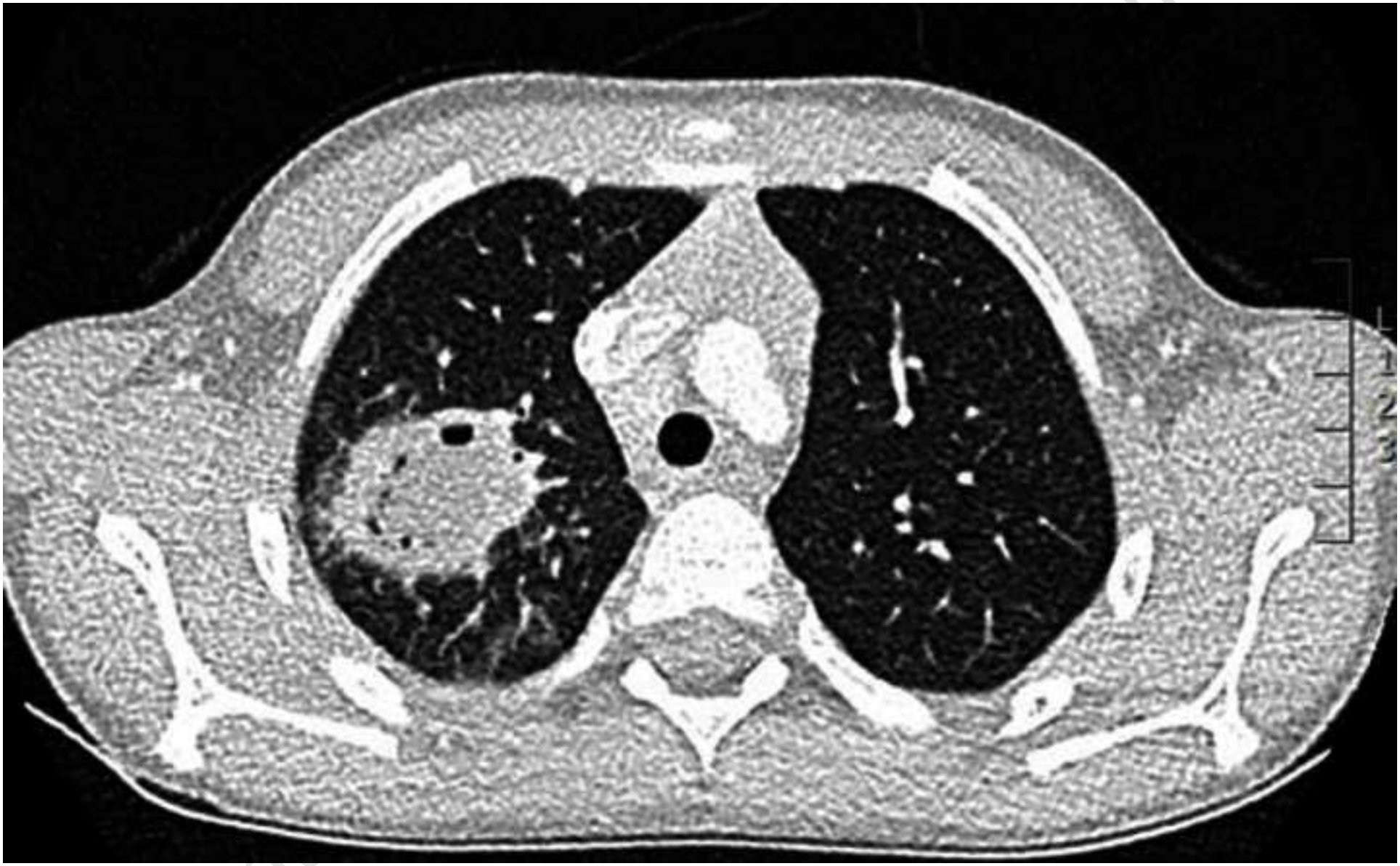

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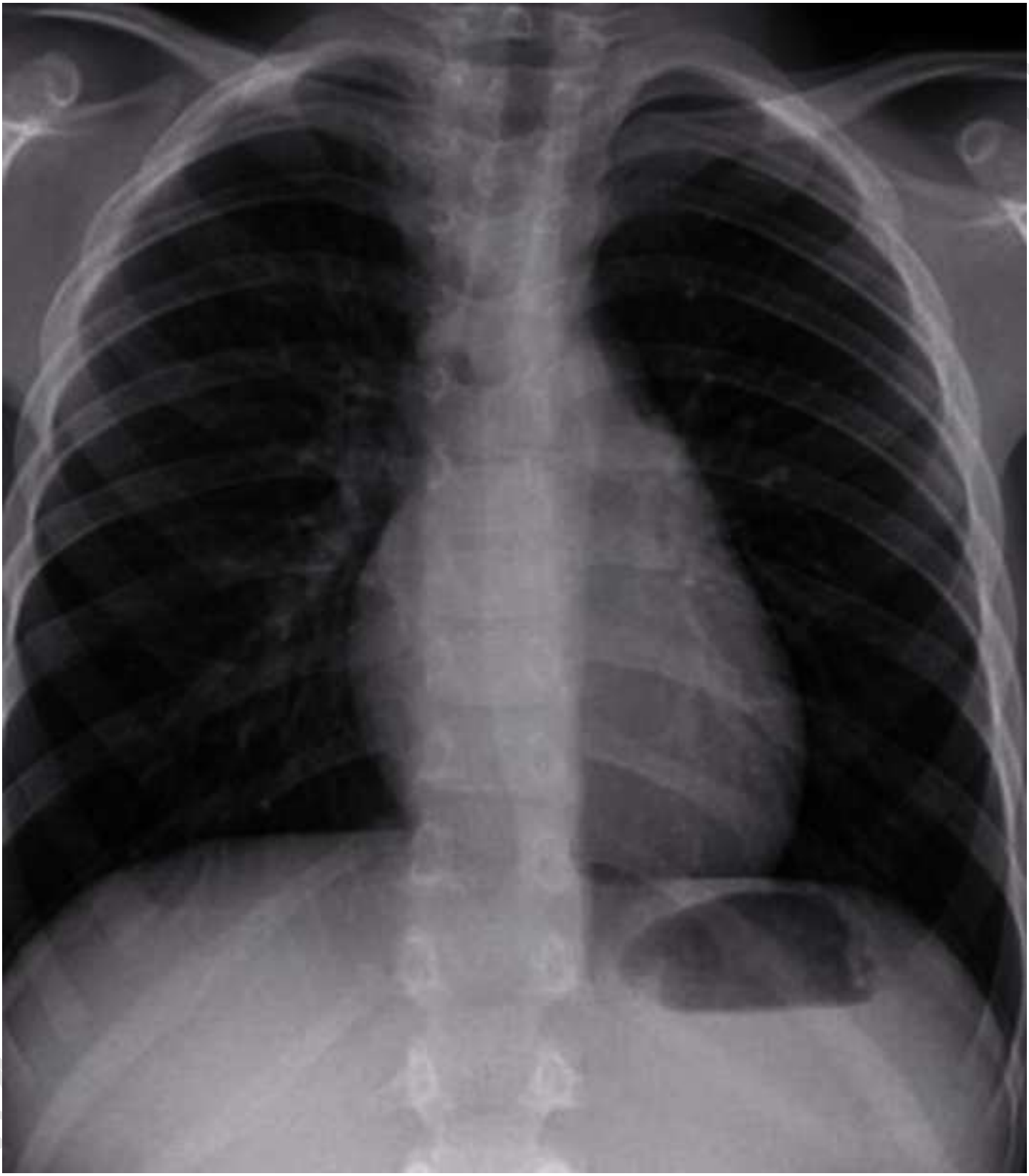

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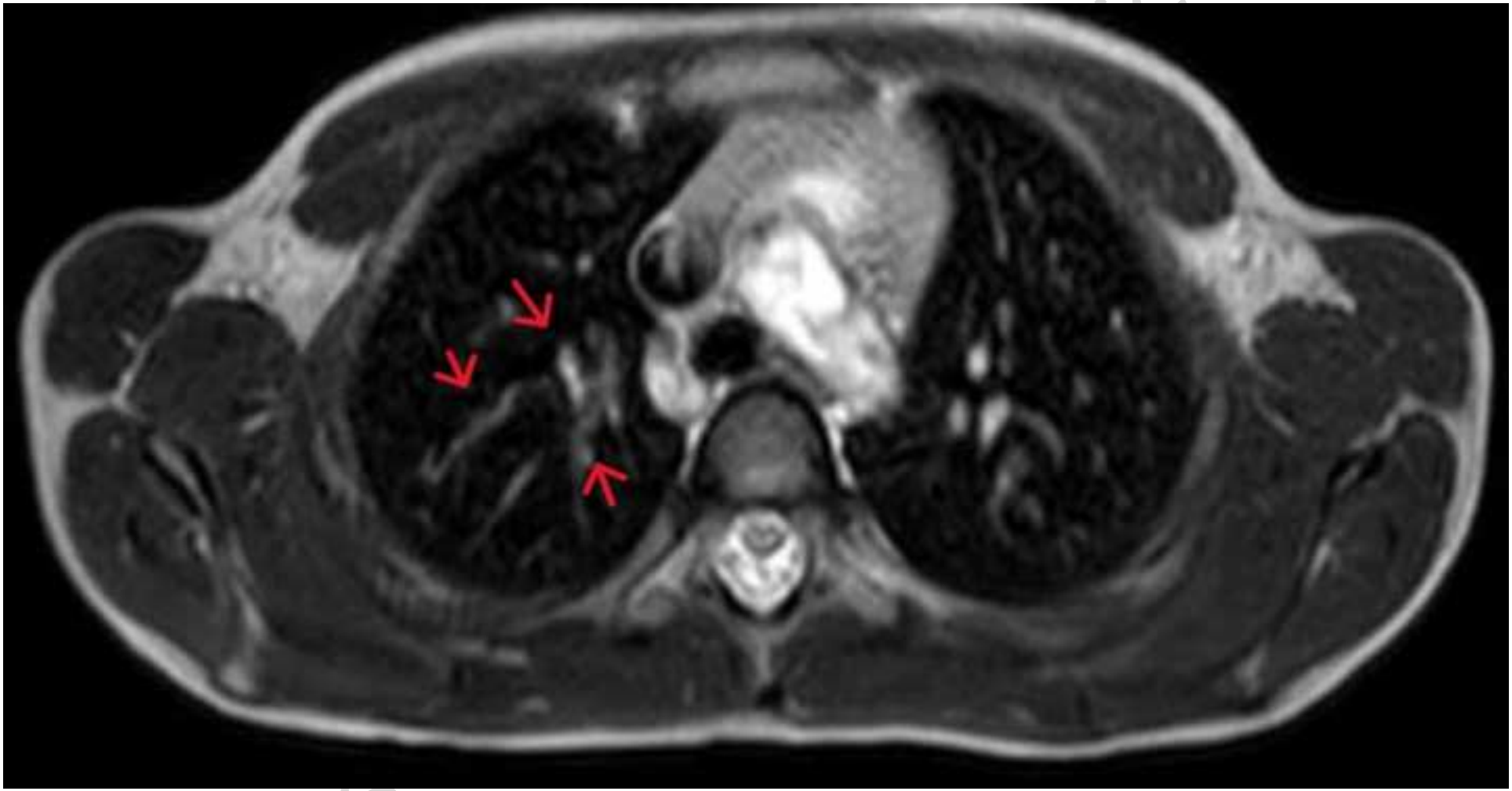

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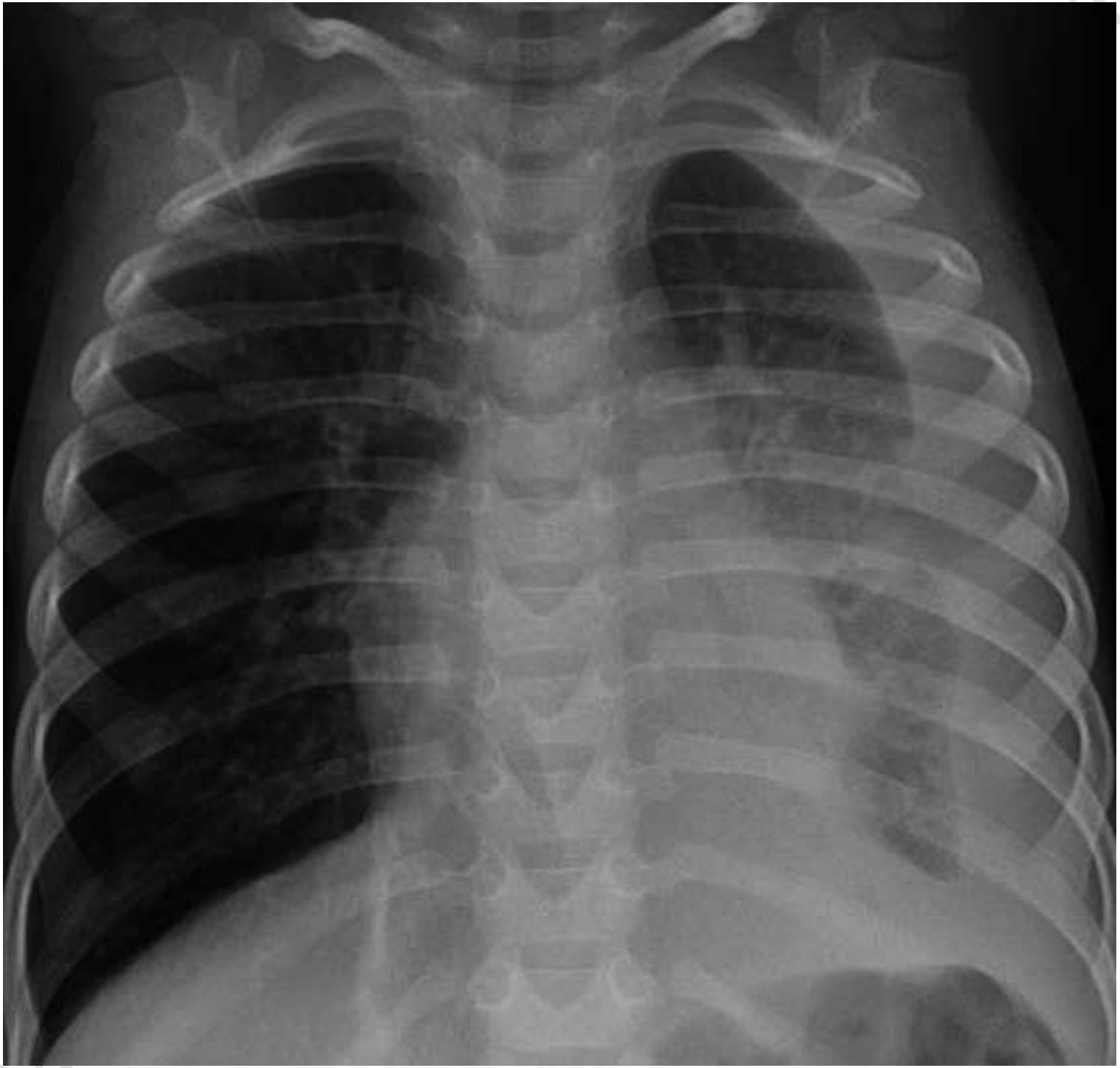

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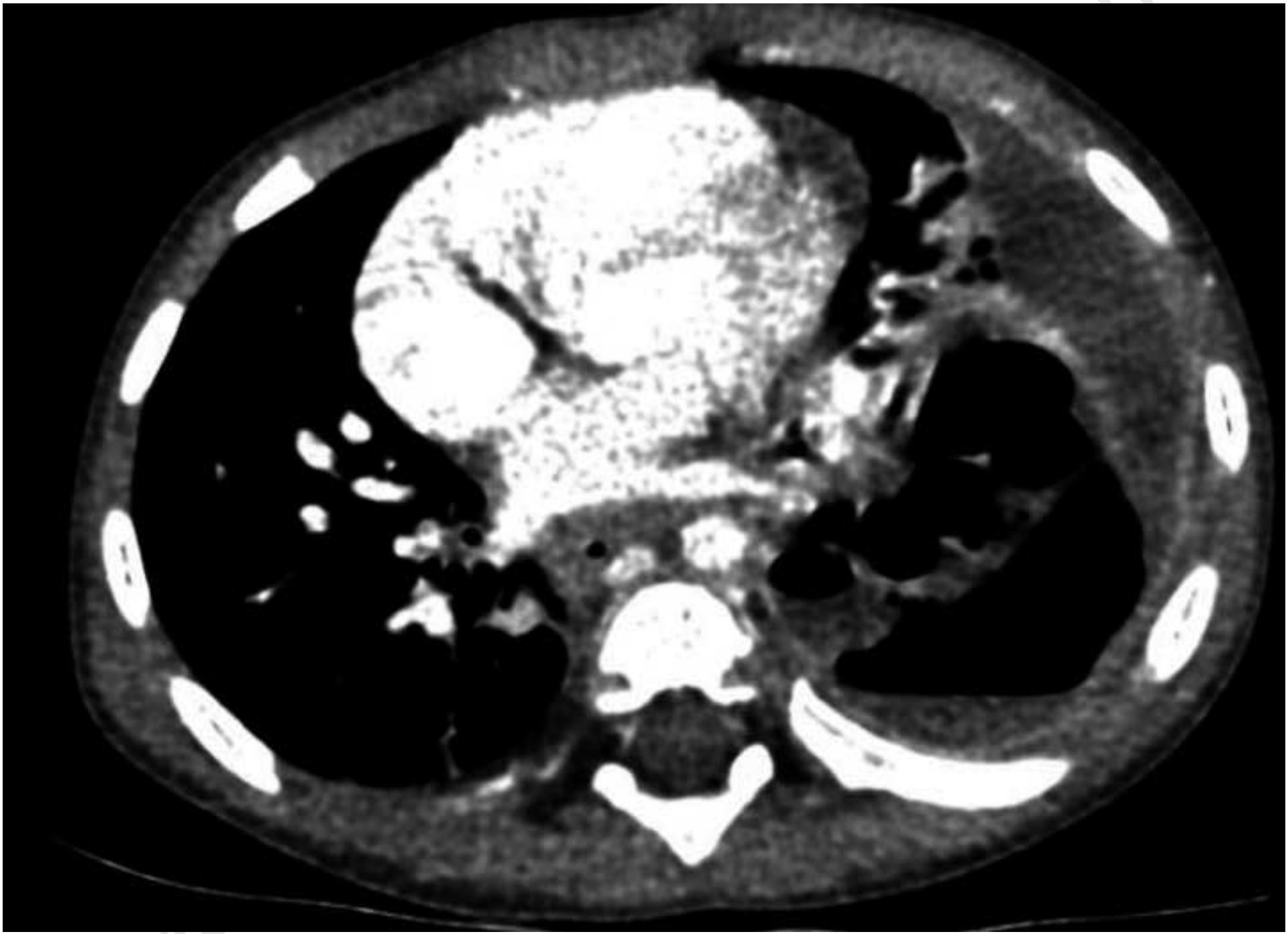

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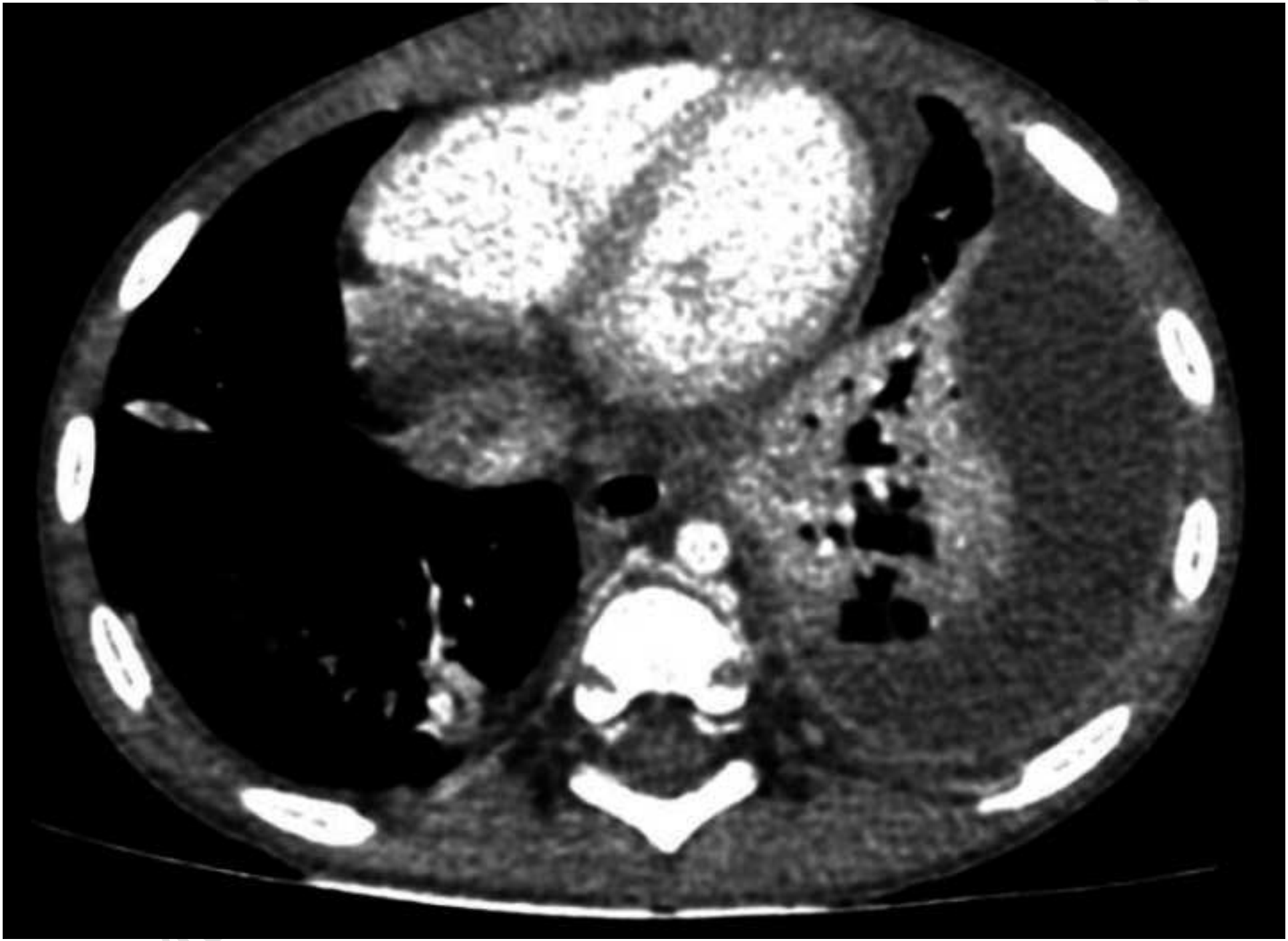

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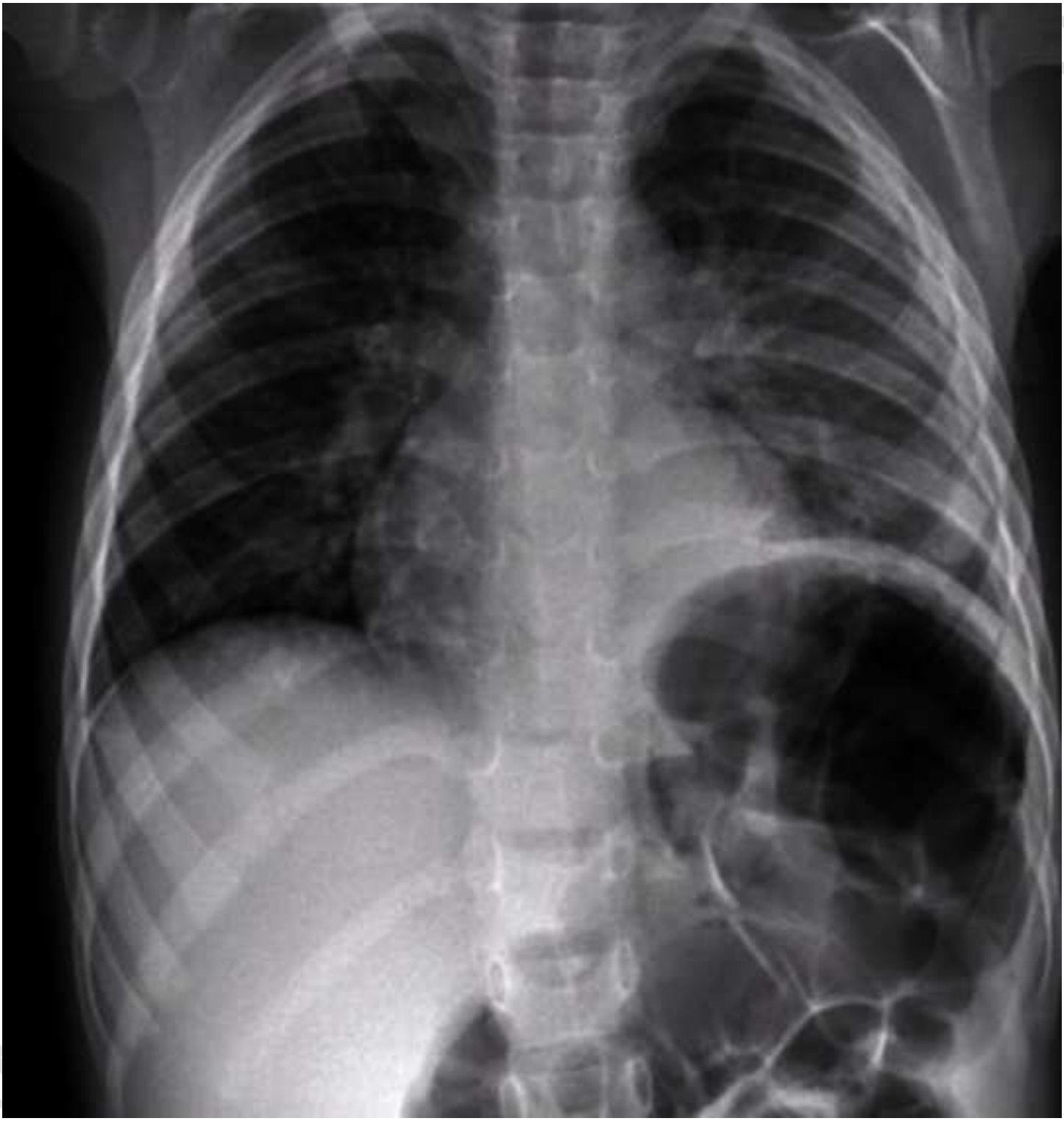

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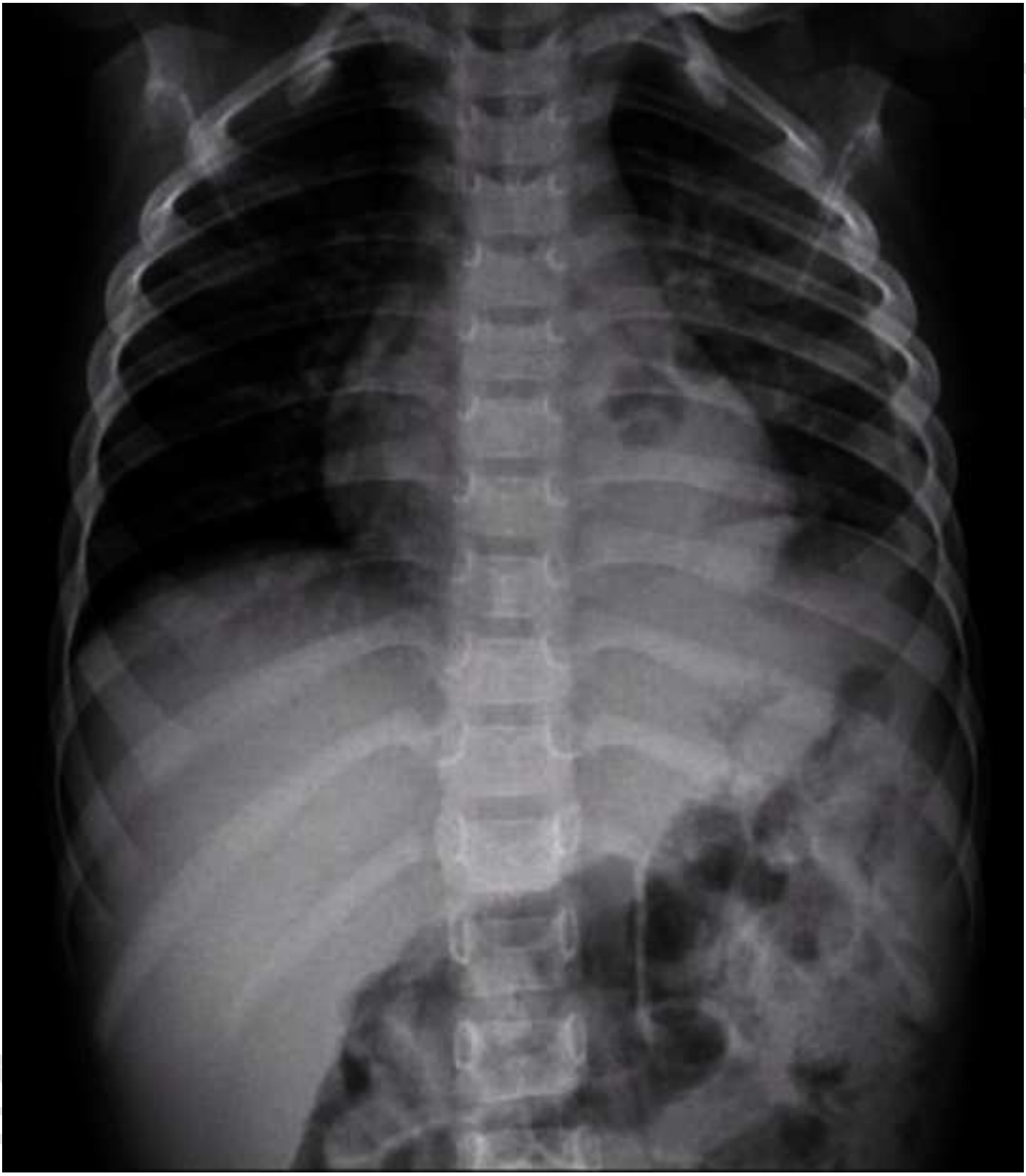

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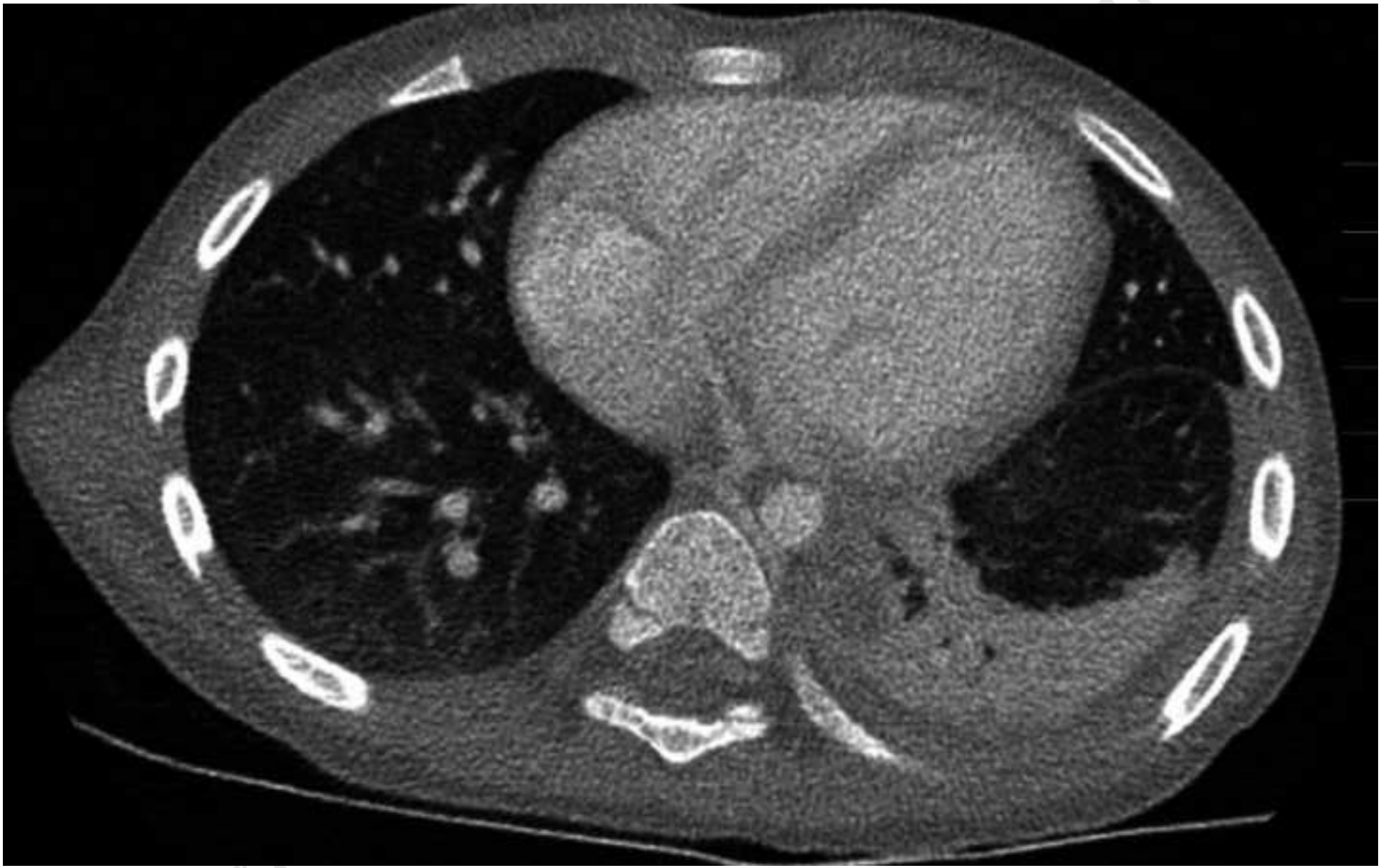

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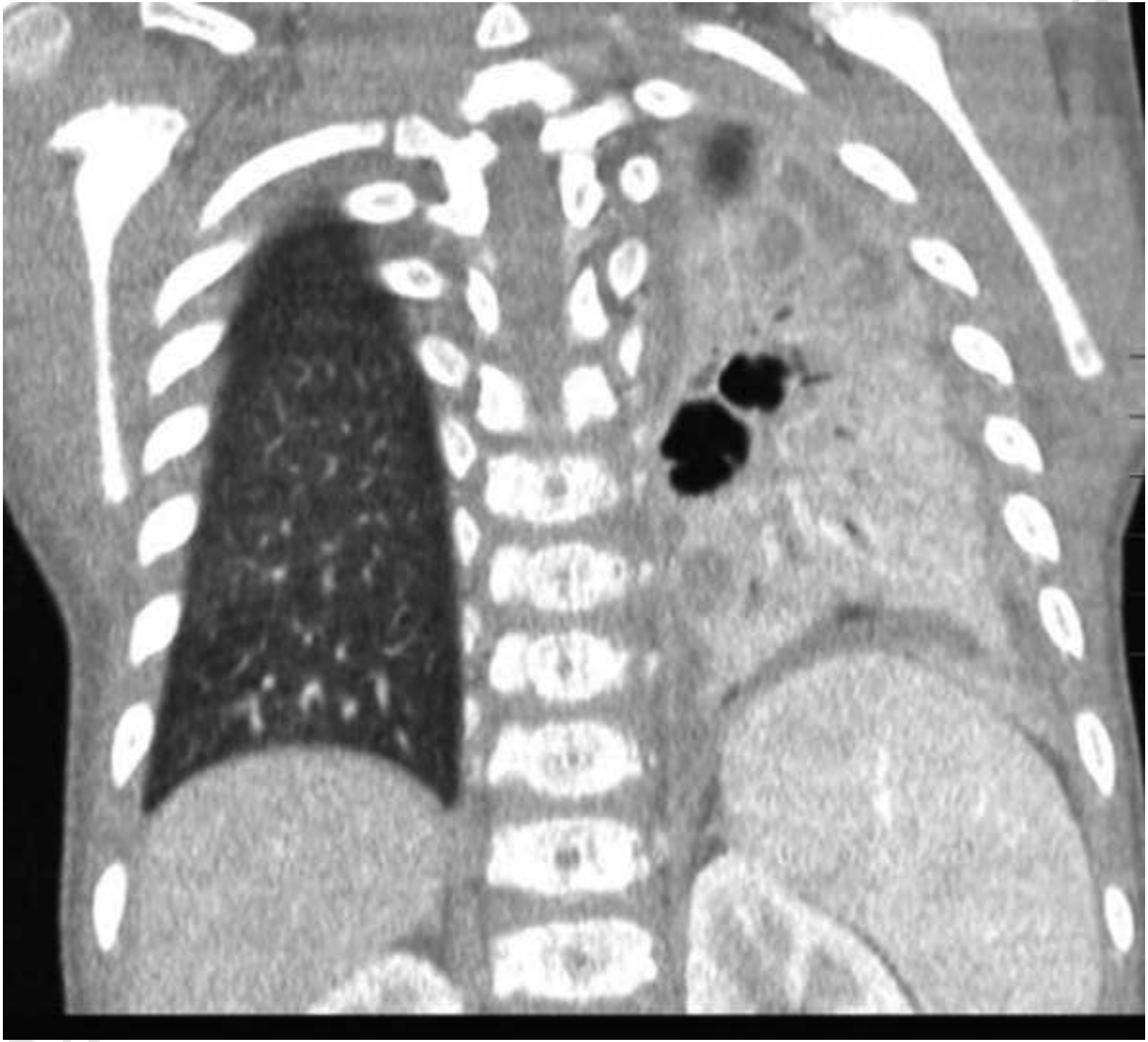

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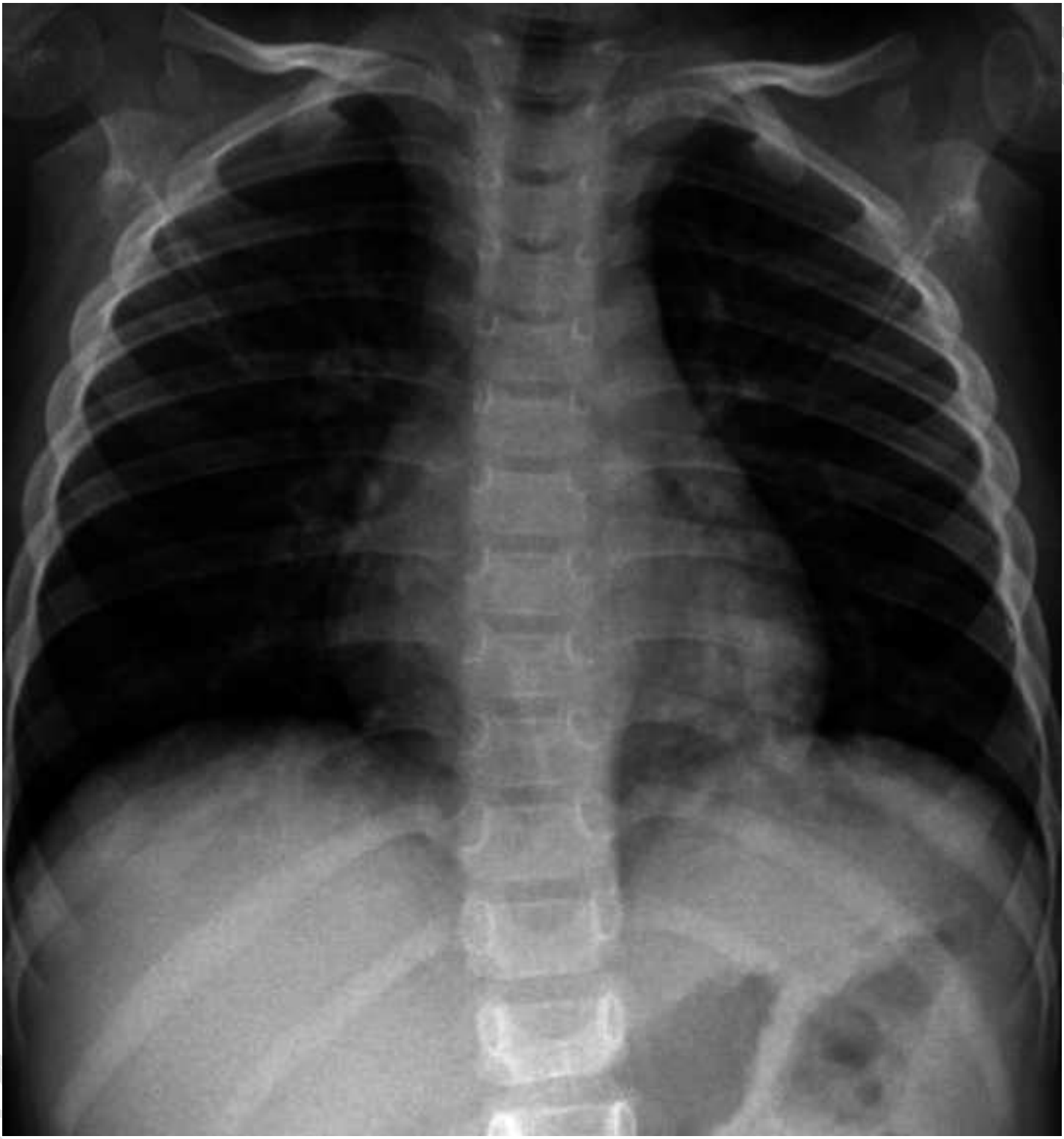

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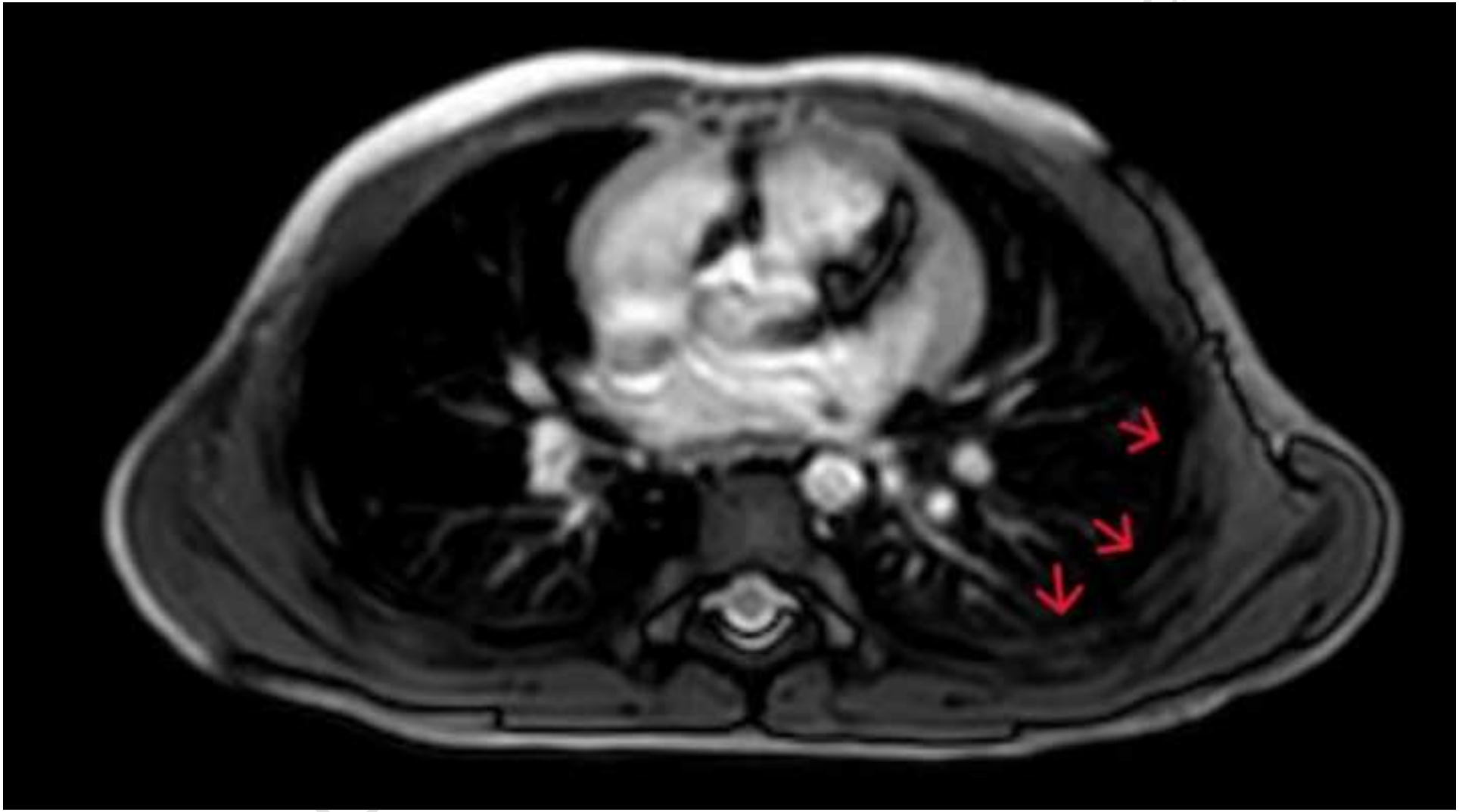

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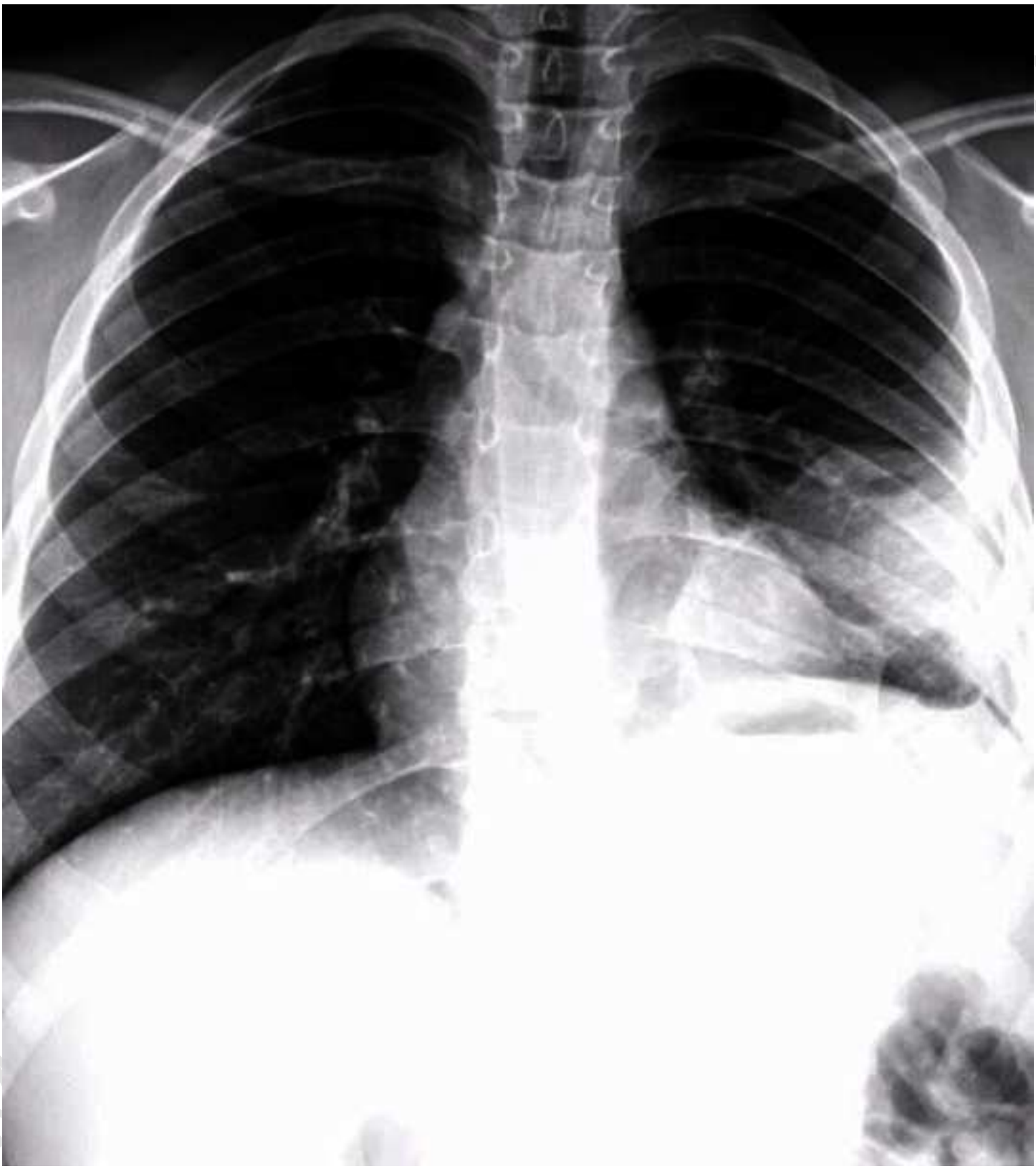

Figure 15

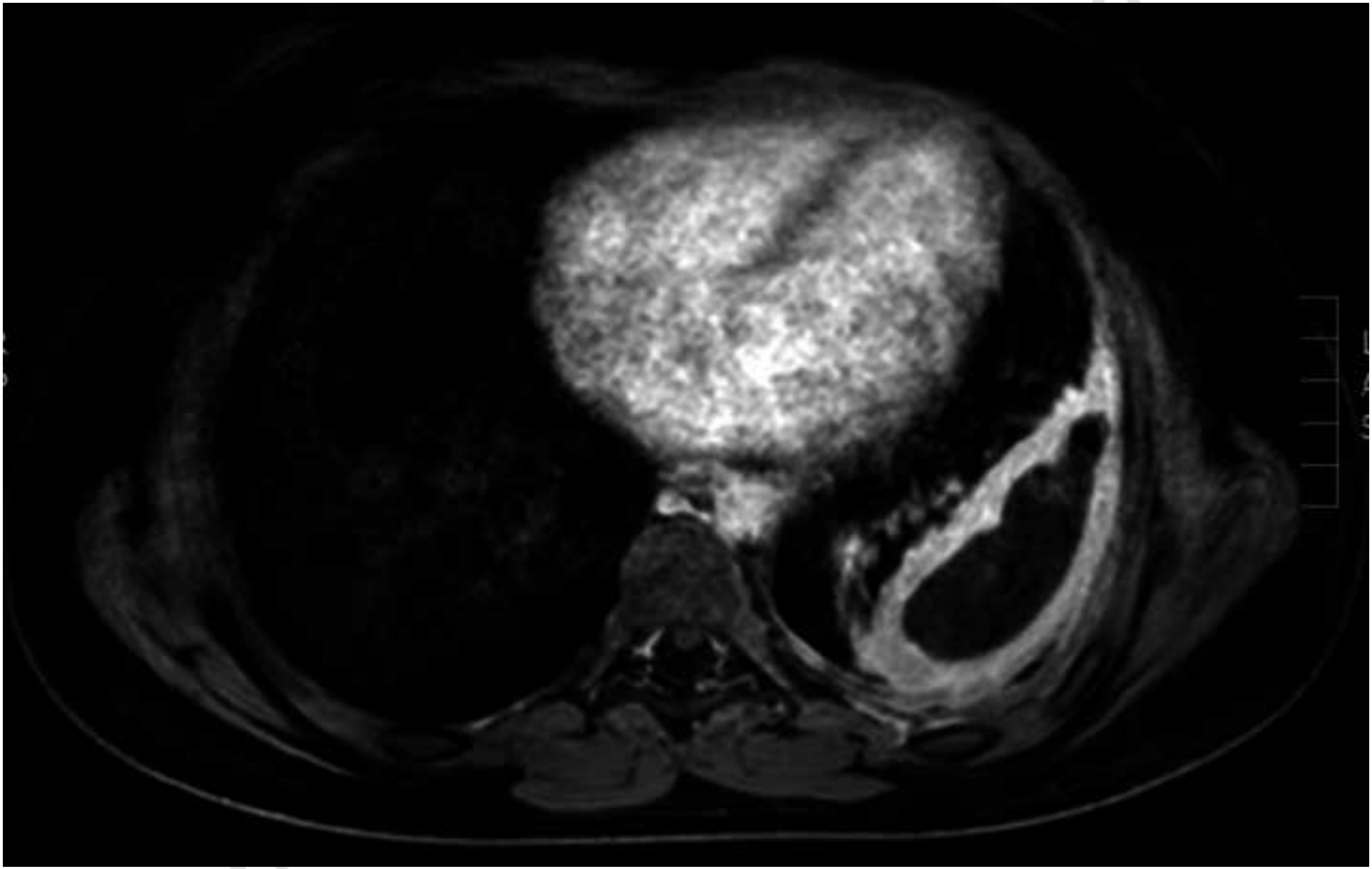

Table 1. *Four cases in comparison.*

	Case 1	**Case 2**	**Case 3**	**Case 4**
Age at diagnosis	8 yo	20 m	3 yo	11 yo
Month of diagnosis	End of august	December	October	September-october
Symptoms at onset	Fever, cough and right-chest pain for 5 days	Dyspnea, low food intake, fever and cough for 3 days	Asthenia and dyspnea on exertion for 10 days, fever and wet cough for 5 days.	Pain in the left hemithorax and fever
Already on antibiotic therapy	No	No	Yes (amoxicillin-clavulanate)	Yes, Piperacillina-tazobactam iv and clarithromycin and amoxicillin-clavulanate po for Chlamydia p. pneumonia
Vital parameters	SaO2 98%; HR 116 bpm; AT 37.3°C	RR 60/70 bpm, SaO2 92%, HR 180 bpm, AT 39.6°C	SaO2 94%, HR 164 bpm, AT 38.1°C	SaO2 97%, HR 138 bpm, AT 38.3°C
Lung imaging report before the diagnosis	**Chest X-ray**: parenchymal thickening in the right upper field. No signs of pleural effusion.	**US:** Left organized pleural effusion with maximum thickness of about 5-6 mm at the midfield and 4-5 mm at the base and pulmonary consolidation.	**US:** Bilateral pneumonia with extensive pleural effusion on the left side.	**US**: Extensive consolidative area left basal lung in the posterolateral location with voluminous central necrotic component with diameter maximum of about 6 cm and thin flap of left pleural effusion
CT report	35 mm thickening in the right upper lobe, with central necrosis and millimeter gas-containing areas	Copious left pleural effusion with maximal thickness of 27 mm, apical-posterior pocket air layer, consolidation in the left lower lobe with areas of colliquative appearance and confluent air cavities, atelectatic consolidation in the left upper lobe, slight shift of the chest towards the right of the midline	Left mid-baseline necrotizing pneumonia	18 mm pleural effusion at the base of the left lung, with thickening of the adjacent parenchymal tissue
WBC, N, CRP	WBC 14,920/mmc, N 63.1%, CRP 105.9 mg/L	WBC 21,940/mmc, N 86.6%, CRP 265.2 mg/L	WBC 17,030/mmc, N 72% CRP 44.4 mg/L	WBC 15,490/mmc, N 70%, CRP 147.5 mg/L
Empirical antibiotic therapy before culture results	Ampicillin sulbactam iv	Ceftriaxone iv	Ceftriaxone iv and clarithromycin po	Piperacillina-tazobactam iv and vancomycin iv
Microbiological tests	Streptococcus pneumoniae (sputum culture)	Streptococcus pneumoniae (blood and urine cultures) Rhinovirus (nasal swab)	Negative (blood culture)	Chlamydia pneumoniae IgA and IgG
Antibiotic therapy iv	Clindamycin and piperacillin tazobactam	Vancomycin and ceftriaxone	Piperacillin-tazobactam and vancomycin	Piperacillin-tazobactam and vancomycin
Duration of antibiotic therapy iv (days)	14	10	24 and 21	28 and 21
Antibiotic therapy po at discharge	x	Cefotaxime	x	Cefpodoxime
Duration of antibiotic therapy po (days)	x	14	x	10
Symptoms at follow up	Reduced tolerance to exercise until 6 months after discharge	No follow-up	No symptoms	Mild and decreasing thoracic pain until two weeks after discharge
Lung function	Increase in pulmonary resistances after 1	No follow-up	Obstructive pattern after 8 months.	Mild increase in pulmonary resistance

	Case 1	Case 2	Case 3	Case 4
	month from the discharge, markedly reduced after 6 months.		Normal pattern after 10 months from the discharge	and reduction in vital capacity after 1 and 3 months, which normalized after 6 months from the discharge
Long-term radiological follow-up	**MRI** (after 6 months)**:** Minimal residualperibronchial inflammatory component in the area of the previous lesion, reactive lymphnodes at right perilateral site.	Not done	**MRI** (after 10 months)**:**Minimal pleural thickening in posterior parietal location with associated thin striae with a fibrotic appearance.	**Ches x-ray** (after 6 months): normal

WBC: white blood cells, CRP: c-reactive protein, US: ultrasounds, CT: computed tomography, yo: years old, m: months; iv: intravenous, PV: predicted value, TPR: total peripheral vascular resistance. AT: auricular temperature, bpm: beats/breaths per minute; N: neutrophils, po: oral, MRI: nuclear magnetic resonance; T1: after 1 month from the discharge; T2: after 6 months from the discharge. CRP laboratory cut-off level > 10 mg/L.