Parapneumonic Pleural Effusions Consist of Two Distinct Entities

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Abstract: Pleural effusions (PE) complicating pneumonia are usually considered as one entity. But some effusions collect from the start of pneumonia (“sinpneumonic”-SPE), others appear after antibiotics have been started (“metapneumonic” – MPE). Material, methods. It is a retrospective clinical study (1980-1990s); with new therapies tested over next 20 years. Included are 2561 children with pneumonia (1 month – 14 years); 424 of them had PE, classified as SPE (173) or MPE (251 – 59%). Usual labs and immune complexes levels in blood and PE were studied. Results. Of 281 positive PE *S. pneumoniae* was identified in 88%, *H. influenzae type b* – 5%, *S. pyogenes* – 8%, *S. aureus* – 4%. MPE was mostly seen in necrotizing pneumonia in under-5 children, particularly with antibiotics started late-after 4th day. MPE starts with initial short drop of temperature that recurs to 39,5-40,5°C and lasts 5-20 days, refractory to antibiotic changes. PE are always serous or serous-fibrinous with WBC <1000/mm³, pH>7.3, glucose >3.0 mmol/l; X-ray show costal pleura fibrin deposition. Initial blood WBC, CRP, procalcitonin levels are elevated, normalizing with necrotic pneumonia resolution. From this point ESR rapidly rises to 40-80 mm/h – a landmark of MPE. We found a much higher levels of pneumococcal antigens containing immune complexes with complement consumption in MPE, compared to SPE – in both blood and PE. This suggested an immune mechanism of MPE and justified the administration of steroids (prednisolone 1 mg/kg/d for 2-4 days) that stops fever within 1-2 days (100% cases). Full fibrin resorption occurs in 1-2 months, rarely more, making unnecessary fibrinolysis, drainage or thoracoscopy. Conclusions. MPE is an immunopathologic complication of pneumonias’ antibiotic treatment that results from microbial cells destruction by antibiotics liberating an antigen excess favoring immune complexes formation, pleura being the shock organ. Recognition of MPE is paramount for the therapy choice, particularly – steroids, and for reducing invasive procedures.

Keywords: Pneumonia, Pleural Effusion, Immune-mediated Mechanism, New Treatment, Reducing Invasive Procedures

1. Introduction

Pleural effusions that complicate pneumonia in children are usually described as one entity-“parapneumonic” pleurisy [1-3]. Their development is classically described as going through “exudative, fibrinopurulent and organizing phases” [4]. Some authors distinguish complicated and simple parapneumonic effusions-however, without pointing out differences in their origin. Simple parapneumonic effusions have pH > 7.2 and glucose > 2.2 mmol/l, no organisms in culture or gram stain and no need for pleural fluid drainage [5]. In our experience these effusions develop after antibiotic treatment had been started and they differ in origin from “complicated effusions”.

This difference also follows from a randomized trial of PE

steroid treatment (dexamethasone 1 mg/kg/day for 2 days + antibiotic) by A. Tagarro with co-workers [6]. The median time to recovery (normal temperature, SaO₂ and general state) for patients with “simple effusions” treated with a steroid was 76 hours (3.1 days) shorter than for patients with those receiving placebo (P=0.017). For patients with “complicated effusions” the difference to recovery was only 14 hours (0.5 days).

The purpose of this article is to show that pleural effusions developing after the start of effective antibiotic therapy (we call them “metapneumonic”-MPE), fundamentally differ in their origin from those accompanying pneumonia from its inception (“sinpneumonic”-SPE). It is also intended to demonstrate that MPE require different therapeutic approaches.

2. Material and Methods

It is an observational clinical study, an intensive phase of which with studies of effusions' properties was conducted in 1980-1990-ies. Our research remained largely unknown abroad being published only in Russian journals (indexed in PubMed without abstracts [7-9]) and monographs; some of the results we presented at Europediatrics and WSPID meetings.

During almost 40 years long period, of 2561 children (aged 2 month – 14 years) hospitalized with community acquired X-ray positive pneumonias (CAP) 424 (17%) had pleural effusion. The percentage of CAP complicated by pleural effusion decreased from 17% in the years 1979-1989 to 1.5% later on and rose back to 8.3% from 2008 (in under-5 children it was 23-30%). Of 424 CAP complicated by an effusion 173 were classified as SPE and 251 (59%) as MPE.

At an early stage we used a standard practice of pleural tap in all patients with effusion. Exudates were studied by routine chemical tests, by culture and/or bacterial antigens detection (latex agglutination, countercurrent electrophoresis). We also studied concentration of circulating immune complexes in both blood and pleural exudates. For the last 20 years we developed a patient-friendly approach: pleural punctures were performed only to remove large effusions, thus we had no effusions to analyze.

3. Results

3.1. Etiology

The majority of pleural effusions are found in pneumococcal pneumonia. Of 281 positive exudates *S. pneumoniae* was identified in 88%, *H. influenzae type b* – in 5%, *S. pyogenes* – in 8% and *S. aureus* – in 4% (the young infants with higher *S. aureus* frequency were usually hospitalized in neonatal departments). These data do not differ from published figures before introduction of pneumococcal mass vaccination [10]. Of 102 *S. pneumoniae* strains typed 28 were type 1, 23 – type 7, 14 – type 3, 11 – type 14. Over 1/3 of effusions were sterile.

Pleural effusions are more likely to complicate necrotizing pneumonia – X-ray evidence of lung destruction (usually bullae) we found in 23% of children with SPE and up to 80% of MPE, the rest being with massive lobar or bilateral infiltrates.

3.2. Sinpneumonic Effusions (SPE)

Sinpneumonic effusions (SPE) are either purulent or fibrinopurulent. Its WBC count is 2000-10000/mm³, pH <7.2, glucose <2.2 mmol/l. They correspond to what some authors describe as “complicated parapneumonic effusions” [5, 6]. Being the result of microbial inflammation SPE usually respond to appropriate antibiotics if started early enough and do not progress to empyema.

3.3. Metapneumonic Effusion (MPE)

In the past this term had been infrequently used to denote either pleural effusions that last beyond pneumonia [14] or sterile pleural effusions [12]. MPE are mostly seen in necrotizing pneumococcal pneumonia (predominately among under-5 children), particularly when antibiotic treatment is started late-after the 4th day of the disease. In some cases, it develops in patients with CAP complicated by SPE (see case 2). Rarely MPE is seen in CAP caused by *S. pyogenes* and *H. influenzae b*.

A characteristic feature of MPE is a drop of temperature 1-2 days after the start of antibiotics indicating that a bactericidal effect has taken place. It lasts usually for 12-24 hours, then fever recurs reaching 39,5-40,5°C and lasts for 5-20, mostly 7-14 days. Fever caused by necrotizing pneumonias usually last till the discharge of lung necrotic material and bullae formation, but MPE is also present “non-microbial fever” continues beyond this event, non-responsive to change of antibiotics. With time periods of fever gradually shorten to 3-5 hours a day; concomitantly the state and appetite of patients improve. Another striking feature of fever in MPE is its steroid sensitivity; it abates hours after their administration (usually oral prednisolone).

On X-ray (usually repeated because of fever rebound after the start of therapy) MPE usually has a characteristic vertical border delineating fibrin sedimentation on costal pleura (see Case 1). When MPE develops after SPE it causes an increase in the exudates' volume (see Case 2). MPE can collect in interlobar spaces. In some cases a reduction of pneumonia infiltrate can be seen testifying to the effect of antibiotics. The resolution of a necrotic infiltrate leaves usually air-filled cavities – mostly thin-wall bullae, sometime with a fluid level; they are usually seen through the exudates. (see Case 3).

The composition of MPE are quite distinct from that of SPE; it is always serous or serous-fibrinous and never turns purulent (except in pyopneumothorax). Its WBC count never exceeds 1000/mm³, pH >7.3 and glucose >3.0 mmol/l; it is sterile though microbial antigens could be demonstrated. When MPE complicates pneumonia with SPE it transforms from purulent to serous-fibrinous (see Case 2). The fibrin layer thickness initially may reach 3-5 cm, it begins to thin even before the effervescence at an average rate of 2-10 mm per week depending on blood fibrinolytic activity (it is often low or zero). Ultrasound may show a small pericardial effusion.

Blood WBC count at the start of MPE is usually high, as also CRP and procalcitonin (PKT) reflecting microbial inflammation in lung tissue. Their normalization occurs with the appearance of air-filled cavities on X-ray. Noteworthy is the dynamics of ESR| it is usually moderately increased at the start of MPE and then it quickly rises; after the clearing of the lung X-ray and fall in WBC count ESR can reach the levels of 40-80 mm/h – a landmark of MPE never seen in SPE. Very high ESR allows to diagnose MPE when the timing of effusion and earlier X-ray results are not known.

The above features suggested an immune mechanism of MPE, presumably associated with immune complex formation. We found much higher levels of circulating immune complexes in both blood and exudates of MPE patients compared to those with SPE. In patients with necrotizing pneumonia and MPE immune complexes' levels (in OD-optical density) were 240 and 65 respectively, whereas in SPE – 140 and 39. Similar differences were found between MPE and SPE complicating non-necrotizing CAP – (differences significant at $p < 0.05$ level). Formation of immune complexes in MPE was accompanied by a massive complement consumption. By splitting immune complexes, we demonstrated the presence in them of pneumococcal antigens.

The described features of MPE allowed us to postulate that its origin stem from a massive destruction of microbial cells by a bactericidal antibiotic liberating an antigen excess that favors formation of immune complexes with pleura as a shock organ.

Figure 1. (X-rays of Case 1). A: Bilateral lower lobe infiltrates. B: Day 3 of treatment-massive pleural effusion with a vertical medial border. C: on day 10 air-filled cavities with some fluid within necrotic infiltrates bilaterally (arrows), receding layer of fibrin in the left pleural cavity.

Follow-up for 2-4 years shows a good recovery of conservatively treated patients with MPE complicating CAP, including the necrotizing ones. In some children less than 4 years of age at a time of CAP we find a minimal thickening of pleura on X-ray, a mild-to-moderate (around 10%) decrease in the pulmonary blood flow in the previously affected lobe on a scintigraphy, a slightly (-1 SD) lowered spirometry parameters and diffusion capacity with a minimal increase of dead space due to V/Q mismatch.

The following cases illustrate findings described above.

Case 1. A 11 months old girl admitted on the 10th day of high fever with bilateral lower lobes' CAP (Figure 1-A), WBC count of $18\,000/\text{mm}^3$ and ESR 7 mm/h . Benzylpenicillin i.v. resulted in a fall in temperature for 18 hours with a return to $39\text{-}40^\circ\text{C}$. X-ray on the 3d day of treatment (Figure 1-B) revealed a massive pleural effusion left, its puncture yielded 140 ml serous-fibrinous fluid with WBC $450/\text{mm}^3$, pH 7.35 and glucose 3.8 mmol/l ; *S. pneumoniae* serogroup 19 was identified by latex-agglutination. On the day 10 there was a bout of irritability and productive cough, on X-ray (Figure 1-C) air-filled cavities appeared bilaterally some with a fluid level; the layer

3.4. Treatment of CAP Complicated by MPE

Since MPE is a result of effective antibiotic therapy (i.v. benzylpenicillin, amoxicillin/clavulanate or ceftriaxone) we continue them till normalization of WBC count and CRP switching to an oral analog after 5-7 days. They are combined with oral prednisolone 1 mg/kg/day for 3-5 days. Rapid improvement obviates the need for pleural puncture, drainage or thoracoscopy. We found the fibrinolysis to be unnecessary since full resorption of fibrin occurs in all cases though it may take 1-2 months. Early administration of steroids-before resolution of necrotizing pneumonia (8-14th day of MPE) requires explanation to parents – without it steroids may be presumed to be a cause of a “lung destruction-bullae formation”. We give steroid earlier if parents could be convinced in its safety. We discharge MPE patients after effervescence with steroids and follow them as outpatients if needed.

of fibrin receded. WBC sank to $12500/\text{mm}^3$, ESR rose to 25 mm/h . Antibiotic was switched to V-penicillin for another week. Temperature normalized on days 19 when ESR rose to 60 mm/h and there was a marked thinning of fibrin layer on a discharge X-ray on day 21 (not shown). Dx: Necrotizing CAP, MPE, natural course without steroids (from year 1988).

Case 2. A 1 year old boy admitted on the 4 day of fever $38\text{-}39^\circ\text{C}$. On X-ray (Figure 2-A) – pneumonic infiltrate complicated by SPE right. Pleural tap: purulent exudate with WBC $5000/\text{mm}^3$, pH 7.12, glucose 2.0 mmol/l , *S. pneumoniae* on culture. On day 2 on i.v. cefazolin temperature fell to normal for 1 day and then rose to $39.5\text{-}40.2^\circ\text{C}$. X-ray on day 3 (Figure 2-B): an increase of effusion to the 1st rib. The repeated tap: serous exudates typical of MPE with WBC $700/\text{mm}^3$, pH 7.4, glucose 3.9 mmol/l . Blood WBC decreased to $8000/\text{mm}^3$ from $11000/\text{mm}^3$ on admission, ESR rose from 20 to 42 mm/h . Antibiotic was discontinued on day 6 when prednisolone (1 mg/kg/d for 3 days) was given. Fever abated next day, discharge on day 9 with normal blood analysis. Resolution of CAP and pleurisy documented on day 30. Dx: CAP complicated with SPE with MPE.

Figure 2. (Case 2). A: Right lower lobe pneumonic infiltrate, pleural effusion to the 3d rib. B: day 3 of treatment – pleural exudates increased in volume over the 1st rib.

Case 3. A 5 year old girl admitted on the 5th day of a severe CAP with fever up to 40.1°C, WBC 13200/mm³, neutrophils 11000/mm³, CRP 290 mg/l, PKT 13 ng/ml and ERC 20 mm/h. X-ray (Figure 3-A) showed a right upper lobar infiltrate with a denser lower part predicting a necrotizing pneumonia. Amoxicillin/clavulanate i.v. 90 mg/kg/d was started and, on day 2 X-ray (Figure 3-B) showed the beginning of MPE accumulation. Prednisolone 2.8 mg/kg/d i.v. for 3 days was added. The fever abated by the end of day 2 and the next 4 days was below 38°C with 2 short picks on days 4 and 6 when oral prednisolone 1

mg/kg/d was given. From day 4 our patient, after a bout of productive cough felt much better, was active with a good appetite and no complaints. X-ray on day 6 (Figure 3-C) showed a layer of pleural exudates covering right lung without mediastinal shift and an air-filled cavity with some fluid in the upper lobe. CRP fell to 11 mg/l, ERS reached 65 mm/h on day 6 and dropped on day 8 to 11 mm/h. The girl was discharged on day 8, X-ray on day 30 (not shown) revealed only increased lung markings in the right upper lobe and no effusion. Dx: necrotizing CAP, MPE. Early steroids considerably shortened its course.

Figure 3. (Case 3). A: right upper lobe infiltrate with a half-round lower border of a higher density part suggesting future necrosis. B: day 3 of treatment – the beginning of exudation seen on the right costal border. C: day 6 – an air-filled cavity with a fluid level at the bottom of affected lobe (arrow), pleural exudates enveloping right lung with some fibrin sediment.

Case 4. A 2 years old boy was admitted to another hospital for a CAP of the entire right lower lobe (Figure 4-A). In spite of intensive 17-day treatment with ceftriaxone (9 days), amikacin (7 days) and linezolid (4 days) high fever persisted, in spite of WBC count and CRP normalization on day 6 (from 14000 mm³ and 250 mg/l respectively). ESR rose from 30 to 55 mm/h on day 16. Air-filled cavities in the affected lobe and fibrin depositions on costal pleura appeared on X-ray on day 8 (not shown) and looked more spectacular on

computer tomography on day 16 (Figure 4-B). Following consultation prednisolone 1.1 mg/kg/d was started on day 17 with the drop of temperature after a few hours and sinking of ESR to 9 mm/h on day 18. Discharge on day 20. Follow-up after 7 months: no complaints, no abnormal physical signs and symptoms. Computed tomography (yielding to parents' insistence) found only a linear thickening in the previously affected lower lobe (Figure 4C). Dx: necrotizing CAP, MPE, late but effective administration of steroids.

Figure 4. (Case 4). A: Infiltrate of the right lower lobe. B: Computed tomogram on day 16 –multiple air-filled cavities in a still infiltrated right lower lobe, a layer of fibrin on costal pleura. C: follow-up computed tomogram at 7 month – full resolution of pneumonia and pleural effusion with only a linear thickening in the previously affected lower lobe (arrow).

4. Discussion

Pleural complications of pneumonia in children are the subject of intensive studies that resulted in a shift in therapeutic approaches in the direction of less invasive tactics – less thoracoscopy, less fibrinolysis, less drainage. [1, 2, 13-15]. Our findings allow to make one step further – to withhold pleural puncture in almost all patients with MPE that could be recognized by its course, clinical and X-ray features.

Clinical and laboratory characteristics of MPE presented conform to our hypothesis of its immune origin closely related to antibiotic/pathogen interaction – in fact a complication of antibiotic therapy. One complication of antibiotics-Jarisch–Herxheimer reaction, is caused by endotoxin-like products released from destroyed cell membranes of microorganisms (mostly spirochetes) killed [16]. We saw such a reaction to amoxicillin in the 3 years old boy with a lobar pneumonia. [17]. Jarisch–Herxheimer reactions unlike MPE develop 2-4 hours after the first dose of antibiotic as a systemic shock-like reaction with a drop in blood pressure, fever, chills, hypotension, tachycardia.

The use of steroids in pneumonia is actively debated up to now without a consensus so far.[18] It is clear that steroids would have the biggest effect in immune pathology-we demonstrated a dramatic effect of steroids in MPE that supports the notion of its different nature from SPE. Similar interpretation explains the results of A. Tagarro et al. cited above⁶ [6] with dexamethasone effective in patients with “simple effusions” and not in those with the “complicated” ones.

5. Conclusions

MPE is an immunopathologic complication of pneumonias’ antibiotic treatment that differs from SPE in its clinical course, composition of exudates, X-rays features and a prognosis. Its recognition is paramount for the therapy choice, in particular for administration of steroids and for scaling down invasive procedures.

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Abbreviations

CAP – community acquired X-ray positive pneumonia (s)
CRP – C-reactive protein
MPE – metapneumonic pleural effusion
PE – pleural effusion
PKT – procalcitonin
SPE – sinpneumonic pleural effusion

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