CASE REPORT

Severe asymptomatic rhabdomyolysis complicating a mycoplasma pneumonia

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SUMMARY

Rhabdomyolysis is a very rare and serious extrapulmonary manifestation of a *Mycoplasma pneumoniae* infection. We describe a case of a 47-year-old male patient who presented with progressive dyspnoea, hypoxaemia and cough during the last 3 days. He had no relevant muscular complaints but was diagnosed with severe rhabdomyolysis for which he was treated with hyperhydration. Molecular diagnostics confirmed *M. pneumoniae* as the causative agent and our patient was successfully treated with doxycycline. Only a few cases of rhabdomyolysis complicating a *M. pneumoniae* infection have been described, mostly in infants. In this case, typical suggestive complaints of rhabdomyolysis were absent suggesting that the complication might be underdiagnosed.

BACKGROUND

Mycoplasma pneumoniae is a fairly common causative pathogen for community-acquired pneumonia in children and adults. Apart from lower respiratory tract symptoms, it is associated with a variety of extrapulmonary manifestations.¹ Rhabdomyolysis has only occasionally been linked to *M. pneumoniae* infections, mostly in paediatric patients.² This severe condition can result in acute kidney injury (AKI) but may be asymptomatic. This case describes an adult patient with an asymptomatic rhabdomyolysis complicating mycoplasma pneumonia. We successfully treated this patient and it is unclear whether it would have resulted in AKI if the rhabdomyolysis had remained undetected.

CASE PRESENTATION

A 47-year-old man without a medical history was referred to our emergency department (ED) by his general practitioner, whom he visited earlier that day with progressive dyspnoea and a productive cough for 3 days. He had a general feeling of illness and a measured fever of 39°C at home. He reported no rigours. Shortly before presentation to the ED, he tried climbing stairs during which he was heavily short-breathed, however he reported no complaints of muscular weakness or pain. Nor had he taken any self-medication or drugs of abuse, and was a non-smoker. He worked at a secondary school where a lot of students were ill at that time.

He reported no recent foreign travelling, sauna or hotel visits, nor had he been in contact with animals.

On physical examination, he was mildly dyspnoeic and tachypnoeic with a breathing frequency of 26/minute and an oxygen saturation of 93% while breathing ambient air. He had a regular and equal heart rate of 127/min, with normal blood pressure and a fever with 39.8°C. Pulmonary auscultation revealed some mild cough modifiable bilateral rhonchi, with slight basal crackles on the left side.

He was admitted by our pulmonologist and empirically treated for pneumonia. Because of a lack of improvement and worsening laboratory results, the internist was consulted the next day. At that time, he still experienced only pulmonary complaints. However, on physical examination, a widespread truncal maculopapular rash without pruritus was noticed (figure 1).

INVESTIGATIONS

Initial routine laboratory investigations showed elevated inflammatory parameters (C reactive protein (CRP) 349 mg/L, leucocytes 9×10^9 /L) as well as a slightly elevated serum creatinine (108 µmol/L) and liver tests (aspartate aminotransferase 58 U/L, alanine transaminase 48 U/L, total bilirubin 30 µmol/L, gamma-glutamyl transpeptidase 59 U/L and lactate dehydrogenase 285 U/L). It showed a remarkable elevation of routinely measured creatine kinase (CK) of 3017 U/L. Blood gas examination at the emergency department unveiled a hypoxaemia with a slight respiratory alkalosis (pH 7.48) and normal bicarbonate. Radiography of the chest revealed an atelectasis on the right and a small retrocardiac consolidation on the left side (figure 2). Blood and sputum cultures and urinary antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae* were taken. Urinary dipstick examination showed

Figure 1 A diffuse maculopapular rash on the trunk at day 2.

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Figure 2 Chest radiograph at admission showing atelectasis on the right and retrocardiac consolidation on the left side.

significant haematuria (+++), some leucocyturia and 1.5 g/L protein.

The next day, levels of CRP (406 mg/L), leucocytes ($14.4 \times 10^9/L$) and CK (8320 U/L) had risen. At this point, the internist was consulted who suggested pneumonia with an atypical pathogen possibly *M. pneumoniae*. Throat swab PCR for respiratory virus antigens and atypical pathogen antigens was performed and remained negative. As the CK levels kept increasing (figure 3), autoimmune serology was performed and turned out negative as well. The bronchial sputum was examined for *M. pneumoniae* antigen and turned positive.

We considered haemolysis as a haematological manifestation of mycoplasma pneumonia or autoimmune disease but was unlikely considering a markedly elevated haptoglobin (4.5 g/L).

Microscopic urine examination revealed no erythrocytes, and the urine was positively tested for the presence of myoglobin as explanation for the significant haematuria on a dipstick examination.

DIFFERENTIAL DIAGNOSIS

At presentation, a common bacterial pneumonia was expected, possibly by *S. pneumoniae*. Legionella pneumonia could not be ruled out at that point.

When the condition of the patient failed to improve on empirical antibiotic therapy, he developed a maculopapular rash and laboratory result showed an unexpected substantially increased CK the differential diagnosis was broadened with atypical micro-organisms, viruses and autoimmune diseases.

TREATMENT

Initially treatment was supportive care with oxygen supplementation, 1.5 L/24 hours saline infusion and empirical antibiotic therapy with benzylpenicillin and ciprofloxacin according to our local guideline for moderately severe community-acquired pneumonia. After the urinary antigen test for *L. pneumophila* was negative and patient's CK increased, therapy was switched to benzylpenicillin and doxycycline to include a coverage of mycoplasma. Saline infusion was increased to 8 L/24 hours and later 12 L as it kept increasing.

OUTCOME AND FOLLOW-UP

After the antibiotic switch, the patient started to improve clinically and oxygen supplementation could gradually be decreased. CK kept increasing to reach the highest point at day 3 (25 422 U/L), afterwards it gradually declined and saline infusion could be tempered. Kidney function remained normal during the whole period of time. The patient could be discharged home in a good clinical condition 9 days after admission. During the outpatient follow-up, he told that he experienced some skin flaking and renewal on his hand and feet during his hospital stay until

Figure 3 Creatine kinase course during 9 days hospital admission.

a week after discharge. The patient's CK levels remained within the reference values on follow-up, thereby excluding occult myopathy.

DISCUSSION

M. pneumoniae is a fairly common pathogen that might result in pneumonia. Mycoplasma is the smallest free-living organism but unlike viruses it does not need a host cell for replication. Due to the lack of a cell wall, it is not visible following Gram staining.

There is a gradual better understanding of its pathogenesis. Once it is attached to the respiratory epithelial cells, it produces hydrogen peroxide and superoxide, resulting in damage to these cells. Many of the pathogenic properties of mycoplasma are believed to be immune-mediated rather than the result of direct injury.¹³

Mycoplasma is transmitted through droplets during close contact with an infected person and has an incubation period of 2–3 weeks.⁴ In a prospective series of 4532 patients with a community-acquired pneumonia, *M. pneumoniae* accounted for 7% of all cases sometimes even higher during epidemics.⁵

The clinical presentation varies dramatically, ranging from asymptomatic or mild self-limiting upper respiratory symptoms to radiographically confirmed pneumonia requiring hospitalisation and even severe complicated pneumonia.⁶

The illness usually starts with an influenza-like illness consisting of a cough, headache, malaise and low-grade fever.¹ A small portion of patients develops pneumonia.⁴ Cough is mostly non-productive and dyspnoea is an uncommon complaint. Contrary to pyogenic pneumonia, a mycoplasma infection tends to have a more gradual onset and more multisystem involvement.⁷

Often the presentation is accompanied by extrapulmonary manifestations like dermatological manifestations ranging from a maculopapular rash to Stevens-Johnson syndrome. Several autoimmune phenomena such as haemolytic anaemia, immune thrombocytopenic purpura, transverse myelitis, Guillain-Barre and acute hepatitis or arthritis have been attributed to mycoplasma infection.¹

Diagnosis is based on early clinical suspicion and PCR of pharyngeal swabs, sputum or serology. PCR appears to be more sensitive early in the course of the infection compared with serology. Neither culture nor serology is practical for rapid detection of acute infection, limiting the utility of these methods to retrospective investigations.⁸

Symptoms generally resolve within 3–4 weeks after disease onset but can be shortened with antibiotic therapy; macrolides and doxycycline are the mainstay of this treatment.

Rhabdomyolysis

Rhabdomyolysis is a syndrome caused by injury to the skeletal muscles and involves leakage of large quantities of potentially toxic intracellular contents into the blood plasma. Trauma, immobilisation and (recreational) drug or alcohol abuse are the most common causes. Several infectious micro-organisms have also been linked to rhabdomyolysis.⁹ The classic triad of symptoms consists of myalgia, generalised weakness and darkened urine due to myoglobinuria. In practice however, presentation varies considerably and is often asymptomatic. In large prospective studies of serologically proven rhabdomyolysis, half of patients did not report myalgia or muscle weakness and a third had no abnormality on physical examination.¹⁰

In most cases, proper history points to a likely cause for rhabdomyolysis like alcohol or drug abuse, heat stroke, infection,

trauma or medication. Physical examination may reveal muscle pain and tenderness, decreased strength, rigidity, crush injuries and hyperthermia or hypothermia.¹¹

The hallmark of rhabdomyolysis is an elevation in CK and other serum muscle enzymes. Most of the time serum CK is elevated at least five times the upper limit of normal with a mean peak of 10.000–25.000 IU/L dependent on the cause.¹² The CK rises within hours after muscle damage onset, a decline is usually seen 3–5 day after cessation of muscle damage with a serum half-life of around 1.5 days. Routine urine testing for haematuria by urine dipstick is likely positive in patients with rhabdomyolysis.¹³ The haem molecule in myoglobin reacts with a urine dipstick and can therefore result in a false positive result for haemoglobinuria. Therefore, a microscopic urinary sediment is recommended in patients with unexpected haematuria.

Possible complications of rhabdomyolysis are AKI, compartment syndrome, electrolyte abnormalities, hyperuricaemia and disseminated intravascular coagulation.

AKI as a complication of rhabdomyolysis has a reported frequency of around 30%–50%,^{12 14} and is lower with CK levels at admission <15 to 20 000 U/L and without concomitant risk factors for AKI such as dehydration, sepsis, hypoalbuminaemia and acidosis.¹² The AKI caused by rhabdomyolysis is multifactorial. The third-spacing of fluid due to capillary injury leads to decreased intravascular volume resulting in activation of the renin–angiotensin–aldosterone system therefore decreasing renal perfusion. The excess myoglobin/haem pigment may cause renal tubular obstruction and is direct nephrotoxic due to the formation of reactive oxygen species.

Mainstay for prevention of pigment-induced AKI is the correction of volume depletion, prevention of intratubular cast formation and the treatment of the underlying cause of rhabdomyolysis. This is done by aggressive fluid resuscitation resulting in increased renal blood flow and thus increasing the urinary flow with consequential wash out of partially obstructing tubular casts. Suggested initial treatment is a 1–2 L/hour saline infusion. If diuresis is established, it should be titrated to maintain a urinary output of 200–300 mL/hour until the level of CK decrease to <5000 U/L.¹⁵ Forced diuresis using mannitol or the alkalisation of the urine is debatable.¹⁶ Loop diuretics might even increase the risk of AKI, but may be used judiciously in the setting of fluid overload. If patients remain oliguric despite adequate fluid resuscitation, then they should be considered as having (pigment induced) AKI and fluid administration should be reduced.

To date, rhabdomyolysis linked to a *M. pneumoniae* infection has only been described a few times and mostly in children. The scarcity of such reports is likely due to under-reporting, because rhabdomyolysis often has none or only limited clinical symptoms. Whether this lack of awareness results in morbidity like renal insufficiency is not known.²

Conclusion

Rhabdomyolysis is linked as serious complication to *M. pneumoniae* infection. A high index of suspicion can limit causative treatment delay for rhabdomyolysis caused by mycoplasma and will therefore limit consequential morbidity like renal insufficiency.

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Learning points

- ▶ Rhabdomyolysis could be associated with *Mycoplasma pneumoniae* infection.
- ▶ Serious rhabdomyolysis does not have to present with severe muscle pain.
- ▶ The mainstay of treatment for rhabdomyolysis is treatment of the causative factor and aggressive fluid resuscitation.
- ▶ Parainfectious rhabdomyolysis should surely be considered in a patient with upper respiratory symptoms in combination with muscle weakness, even though symptoms can be limited.

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