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Fulminant Wegener's granulomatosis with multiorgan dysfunction

Case report

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Abstract: Fulminant cases of Wegener's granulomatosis (WG) with severe lung and kidney dysfunction may resemble pneumonia with sepsis and multiorgan dysfunction. Increased serum levels of antineutrophyl citoplasmic autoantibodies (c-ANCA) and proteinase 3 antibodies (PR3) confirm the correct diagnosis and are essential to start early immunosupressive treatment to improve the outcome. With the emphasis on diagnostic dilemmas, we present a 61-year old patient with fulminant WG, resembling pneumonia with sepsis and multiorgan dysfunction. After antibiotics and supportive measures increased serum levels of c-ANCA and PR3 confirmed the suspicion of WG and adequate immunosupressive treatment improved the patient's condition. We concluded that it is important to include vasculitis in the differential diagnosis of unexplained multiorgan dysfunction, because only early adequate immunosuppressive therapy in combination with other resuscitation measures improves survival.

Keywords: *Acute respiratory failure • Immunosuppressed patient • Wegener's granulomatosis*

1. Introduction

Sepsis is the most frequent cause of multiorgan dysfunction. General resuscitation measures and adequate antimicrobial regimen are essential for a successful treatment. In the case of non-responders, microbiological and clinical data should be reassessed and other etiologies considered [1]. Systemic vasculitis, including Wegener's granulomatosis (WG) are among rare causes of multiorgan dysfunction syndrome of non-infectious origin. In fulminant cases of WG acute severe respiratory and/or renal failure may occur, resulting in a high mortality rate [2]. Early aggressive immunosupressive treatment with cyclophosphamide and high dose methylprednisolone prevents permanent organ damage [2-4]. However, immunosuppressive therapy can be deleterious in patients with concomitant infection and sepsis, which is frequently associated with an immunocompromised host [5-7]. With the emphasis on diagnostic dilemmas, we present a patient with fulminant WG, resembling sepsis with a multiorgan dysfunction.

2. Case report

61-year old woman with a history of treated arterial hypertension, prior ischemic stroke and known allergy for hair-dye was admitted to the hospital with apparent pneumonia due to fever, pulmonary infiltrates on chest roentgenogram, leucocytosis and increased CRP. Two months previously she suffered a short period of flu-like illness with painful knees and ankles. A week before admission dyspnea and fatigue started, accompanied by productive and hemorrhagic cough and during the last 3-4 days low grade fever and edema of the lower extremities. On admission to the hospital syderopenic normocytic anemia (hemoglobin level 50 g/L, hematocrit 0.159 and serum iron 4.9 mmol/L) and renal failure (serum creatinine level 431 μmol/L) were observed. Congestive heart failure with concommitant

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pneumonia was suspected due to pulmonary congestion and infiltates on chest rentgenogram together with the increase of C-reactive protein (CRP) to 190 mg/L. Erosive gastroduodenopathy was found by endoscopic examination of the upper gastrointestinal tract. She received packed red blood cells to correct anemia and antibiotic therapy after sputum was obtained. Cefuroxime1.5 mg every 12 hours iv. and oral azytromycin 500 mg per day were administered. In spite of dual antibiotic therapy pulmonary infiltration persisted and CRP even increased to 265 mg/L after a week. Therefore, she was treated with iv. cefepim, but deteriorated further within the next few days. She was admitted to intensive care unit (ICU). On admission to ICU sudden cardiac death due to asystole occured. After successful cardiopulmonary resuscitation she was mechanically ventilated (assist-control ventilation), receiving 60-100% and positive end-expiratory pressure (PEEP) of 10 cm H_2O with peak pressures of 35 to 55 cm H_2O during first four days. Extensive infiltrations of both lungs on admission chest roentgenogram (Figure 1) in addition to increased serum level of procalcitonin (2ng/ml) and C-reactive protein (267 mg/L) indicated pneumonia, that was accompanied by severe respiratory failure (paO_2/FiO_2 131), metabolic acidosis (arterial blood pH 7,05, bicarbonate 12,5 mmol/L), leucocytopenia (2,13.10^{12}/L), anemia (hemoglobin 62 g/L, hematocrit 19,4%), acute renal failure with anuria and with increased serum urea (44,60 mmol/L) and creatinine (699μmol/L) levels, as well as rhabdomyolysis with increased myoglobin (267 μg/L) and hypoalbuminemia (21 g/L).

Hemocultures, urinocultures and aspirates of the trachea were obtained prior to empiric iv. imipenem due to suspected gram-negative respiratory infection. Iv. infusion of fluids, dobutamine and noradrenaline as well as continuous renal replacement therapy were started. After 48 hours antibiotic therapy was adjusted as coagulase negative staphylococcus aureus and enteroccocus were identified in the aspirates of the trachea, both susceptible to vancomycine. In spite of apparent adequate treatment respiratory and renal dysfunction did not improve after a week. Microbiological reassessment revealed pseudomonas aeruginosa in the lungs and at the tip of the central venous catheter together with coagulase negative staphylococcus aureus, susceptible to imipenem and vancomycine, that were administered in combination. In spite of combined imipenem and vancomycine therapy the clinical response to therapy was poor in the next week; CRP and procalcitonin remained persistently increased. We reassessed the patient's history, admission data, in-hospital clinical and laboratory findings. Systemic vasculitis, a possible rare cause of severe respiratory failure, was suspected. As no clinical signs of upper respiratory tract involvement were present, we did not perform tissue biopsy of this area. There were neither signs of ocular, nor articular involvement. Serum levels of antineutrophyl cytoplasmic auto antibodies (ANCA) were estimated. ANCA test was strongly positive for the cytoplasmatic pattern (C-ANCA) by indirect immunofluorescence assay (titre 1:320) as well as antiproteinase 3 antibodies (PR 3) by enzyme linked immunosorbent assay (ELISA) (406 U/ml), confirming WG with concomitant underlying infection. Iv. methylprednisolone, human immune globulin, and one session of plasmapheresis was administered [4,5,7]. Cyclophosphamide was initiated a few days later, when procalcitonin, a marker of severe bacterial infection, decreased < 0.5 ng/l [5,7,8].

Within the next few weeks the respiratory and circulatory failure resolved, except for renal failure, necessitating chronic renal replacement therapy. After discharge the patient was treated with oral methylprednisolone daily, iv. cyclophosphamide every four weeks and hemodialysis three times per week.

Figure 1. Admission chest roentgenograph.

3. Discussion

The pathological hallmarks of WG are chronic granulomatous inflammation of the respiratory tract, necrotizing vasculitis and glomerulonephritis. The lungs and kidneys are among the most frequently affected organs. In 90% of patients WG is manifested as a mild systemic disease of the upper respiratory tract, which

can easily be overlooked [4,5,10]. When WG evolves to a systemic disease life-threatening pulmonary hemorrhage and necrotizing glomerulonephritis develope, resembling severe pneumonia with sepsis and ARDS or even multiorgan dysfunction [2,6].

Anemia, bilateral alveolar infiltrates on chest radiograph, elevated CRP and leucocytosis, which were all documented in our patient, are among the most frequent findings in WG, but may be associated with other diseases as well such as mitral stenosis, anticoagulation therapy, various coagulopathies, infection, malignancies, collagen vascular diseases, etc. Superadded infection, which may occur in fulminant WG, may cause additional diagnostic difficulties and dilemmas [2,5,7]. Chest roentgenograph is nonspecific, but even a computed tomographic lung scan offers no advantage over chest roentgenograph [2,3,10]. Poor clinical response to adequate antibiotic therapy, points to other possible non-infectious origins of the disease [1-3].

In WG combined testing for ANCA by ELISA and indirect immunofluorescence assay is recommended to increase specificity and sensitivity [10]. The sensitivity of PR-3 positive ANCA is about 90% in active WG and 40% when disease is in remission. The specificity of PR-3 positive ANCA in the diagnosis of WG exceeds 95 %. In general, the presence of high- titer ANCA by immmunofluorescence assay (C-ANCA) combined with confirmatory antigen specific assay for PR-3 (ELISA) in the setting of high index of suspicion for vasculitis is sufficient for diagnosis, even in the absence of tissue confirmation [11].

However, biopsy of an affected organ is desirable, but not always possible. Skin biopsy shows a leucocytoclastic vasculitis, renal biopsy a segmental necrotizing crescent glomerulonephritis without immunoglobulin deposition and lung biopsy a granulomatous inflammation with vasculitis. Open or thoracospic biopsy has a far higher diagnostic yield (up to 90% if specific lesions can be identified) than transbronchial biopsy, which provides diagnostic material in only 10% of cases [2,4,5]. Unfortunately, no bioptic material was obtained in our patient, because during the ICU stay severe clinical condition and continuous renal replacement therapy with the use of heparin, as well as later hemodialysis with heparin three times per week, represented an increased risk of bleeding complication during and after bioptic procedure [1].

Vasculitis, including WG are being recognized more frequently within the last decade. Due to increased awareness of the problem, the incidence of WG is being more than 20 cases per million population [2,3,10].

Early recognition of severe WG is important, because immunosuppressive therapy with glucocorticoids and cyclophosphamide has dramatically changed the prognosis. Before the advent of immunosupresive therapy the mortality rate of WG was nearly 90% during one year, but with immunosuppression about 90% of patients reach remission. Relapses occur in 30-50% during the first five years, but five-year survival rate is more than 80% [6,10].

In our patient we observed significant clinical improvement after combined treatment with methyl-prednisolone, cyclophosphamide, immunoglobulins and plasma exchange. However, the dilemma remained, when to start cyclophosphamide therapy, which can be deleterious in patients with concomitant infection and sepsis [5,10]. In patients with severe systemic necrotizing vasculitis treated in ICU, the majority of deaths are due to sepsis [12]. Severe treatment-related infections occur in approximately 10% of cases treated with cyclophosphamide and are a significant cause of mortality. In addition, the diagnosis of treatment-related infection may be underestimated not only through use of immunosuppressants but also by the disease process itself [7].

The decision to start immunosupressants depends on distinguishing between severe infection and fulminant vasculitis. Increased CRP and leucocytosis or leucocytopenia, but above all increased serum procalcitonin level should be considered as specific and sensitive marker of infection and should be estimated when infection is suspected [5,8,9].

Our conclusions are that vasculitis should be included in the differential diagnosis of unexplained severe pulmonary and/or renal failure, because early adequate immunosupressive therapy, prevents damage of affected organs and improves survival. In fulminant cases of WG with superadded infection early immunosupressive therapy is highly effective on top of other resuscitation measures and antibiotic therapy.

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