A 57-year-old man was admitted to the intensive care unit (ICU) after initial resuscitation and hemodynamical stabilization in the emergency ward (EW), where he presented in a comatose state with shock (blood pressure 60/40 mmHg, heart rate 140 pulses/min, body temperature 36.5°C, respiratory rate 28 breaths/min, O2 saturation 90% on room air). Family members reported that the patient had developed a rash (not further specified) and fever seven days prior to his admission to the hospital.

The rash gradually extended on large areas of both lower extremities. The patient had a 30-year history of multiple sclerosis and a 2-year history of Waldenström’s macroglobulinemia for which he was receiving corticosteroids. He also had a history of fracture of the right hip. He was confined to bed for the last 10 years prior to his admission. The rest of the physical examination on admission showed icteric conjunctivae and decreased respiratory sounds as well as fine crackles in the pulmonary bases. There were extensive, hemorrhagic, necrotic areas of the skin of the lower extremities and the abdomen as well as ulcers and bullae (Figures 1 and 2).

Routine laboratory testing on admission revealed normochromic, normocytic anemia (hematocrit 32.1%), decreased white blood cell count (WBC = 3.38 x 10^3/ìl of peripheral blood) with 89.9% neutrophils, and thrombocytopenia (20 x 10^3/ìl of peripheral blood). The prothrombin time (PT) and INR were increased (16.2 sec and 1.35, respectively). Also, blood urea and direct bilirubin were elevated (66 mg/dl and 2.15 mg/dl, respectively). The serum protein electrophoresis revealed increased gamma globulins (25.4%) and detection of monoclonal IgM ¿ chains. The concentration of IgM was increased (990 mg/dl) while IgG and IgA were decreased (124 mg/dl and < 25 mg/dL, respectively). Chest X-ray films revealed lower lobe atelectasis bilaterally.

- The working admission diagnosis was “septic shock in an immunodeficient patient with Waldenström's macroglobulinemia and multiple sclerosis”. The initial treatment included fluid replacement and inotropic agents, while treatment with antibiotics (intravenous piperacillin/tazobactam 4/0.5 g every 8 hours, vancomycin 1 g every 12 hours, and amikacin 500 mg every 12 hours) was promptly started. The antimicrobial regimen was modified after the results of the cultures became available. Blood and urine specimen cultures were negative. P. aeruginosa was isolated from specimens of the fluid of the cutaneous lesions. The in vitro antimicrobial susceptibility testing showed that the isolate was susceptible to antipseudomonal penicillins, cephalosporins, and carbapenems, aztreonam, aminoglycosides, ciprofloxacin, and colistin. Intravenous meropenem 2 g every 8 hours and ciprofloxacin 400 mg every 12 hours were initiated while amikacin, piperacillin/tazobactam, and vancomycin were stopped. He became gradually afebrile and regained a good level of consciousness the fifth day after his admission.

- The patient developed fever again (up to 39 oC) and shortness of breath the eighth day after his admission. He was intubated to receive mechanical ventilation. Specimens of blood, urine, and bronchial secretions were obtained for culture. A strain of P. aeruginosa that was resistant to antipseudomonal penicillins, cephalosporins, and carbapenems, aztreonam, aminoglycosides, and ciprofloxacin and sensitive to colistin was isolated from the bronchial secretions. Chest X-rays showed findings consistent with an infection of the lower respiratory tract. Intravenous colistin (3 million international units every 8 hours) was added to the antimicrobial regimen. He became gradually afebrile the fourth day of treatment with colistin. He was extubated two days later and discharged from the hospital 18 days after his admission to the ICU.
the hospital in a good clinical condition.

Teaching points

- The most noteworthy point in our case report was that *P. aeruginosa* infection in this patient with underlying Waldenström's macroglobulinemia was manifested with extensive gangrenous, hemorrhagic, bullous skin lesions. Although ischemia due to various thromboembolic causes, autoimmune processes, and severe adverse drug reactions were among the main considerations for differential diagnosis, the presenting symptoms and signs of the patient (hypothermia and shock), his underlying hematological disease, the fact that he was receiving steroids for a long period, and the findings from the routine laboratory testing (decreased white blood cell count but with an increased proportion of neutrophils) oriented us to the direction of a serious infection in an immunocompromised host.

- The initial, empiric therapeutic regimen had a broad antimicrobial spectrum (gram-positive cocci, gram negative bacilli, and anaerobic bacteria). Once culture and antimicrobial susceptibility testing results were obtained, the antibiotic regimen was modified focusing on the isolated strains of *P. aeruginosa*. Due to the severity of the infection, we preferred to use the continuous intravenous administration route of meropenem (6 g per 24 hours) instead of the commonly used intermittent intravenous administration. This decision was based on data from a recent meta-analysis comparing the outcome of patients who received antibiotics administered with the continuous versus the intermittent intravenous route and a systematic review of pharmacokinetic and pharmacodynamic parameters of the two modes of intravenous administration, as well as our previous experience [5-8].

- There have been published cases of patients with Waldenström's macroglobulinemia and hypergammaglobulinemia who developed various types of skin lesions including purpura and hemorrhagic bullae [9-12], yet there was no description in these case reports to such devastating skin lesions observed in our patient. A possible underlying mechanism of the initial development of the lesions in our case may be dermal deposition of IgM globulins and destruction of the skin continuity [9]. We hypothesize that such a skin breach was secondarily superinfected with *P. aeruginosa*.

- Ecthyma gangrenosum was considered as a possibility in the differential diagnosis. This entity occurs usually in immunocompromised patients with *P. aeruginosa* bacteremia. Ecthyma gangrenosum is usually manifested with necrotic ulcerations on an erythematous base [13-15]. However, the published experience suggests that ecthyma gangrenosum is usually localized in non-bacteremic individuals while it may be more extensive in those with bacteremia [13-16]. It should be noted that our patient did not have *P. aeruginosa* bacteremia although blood cultures were obtained prior to the administration of any antimicrobial agents. We believe that the underlying Waldenström's macroglobulinemia contributed to the pathophysiology of the development of the rare skin manifestations of the infection seen in our patient because there have been other reports in the literature of patients with Waldenström's macroglobulinemia and related disorders who had extensive hemorrhagic, bullous lesions [9-12].

- The immunocompromised state of the patient due to the underlying hematological disease and the treatment with steroids probably contributed to the severity of the infection and its manifestation. It should be emphasized that infection consists a major cause of mortality in patients with Waldenström's macroglobulinemia [17,18]. Skin lesions that had some similarity to those observed in our patient, although less diffuse and caused by other pathogens, were reported to have occurred in immunocompromised patients due to an underlying disease and/or immunosuppressive medications [19,20]. Cutaneous lesions of various types including ulcers, plaques, and areas of necrosis have been also reported in patients with multiple sclerosis, but these manifestations are usually related to treatment with interferon beta and develop at the points of injections [21-23].

- In conclusion, we report our experience with a patient with Waldenström's macroglobulinemia and multiple sclerosis who developed extended, gangrenous, hemorrhagic, bullous cellulitis in the abdomen and lower extremities due to *P. aeruginosa* infection. We postulate that the underlying Waldenström's macroglobulinemia contributed to the pathophysiology of the development of the rare skin manifestations of the infection seen in our patient. Appropriate antimicrobial treatment including continuous intravenous administration of meropenem (6 g every 24 hours) led to the cure of the infection.

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References