CASE REPORTS

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Acute meningoencephalitis in a patient with systemic lupus erythematosus

Akutni meningoencefalitis kod bolesnice sa sistemskim eritemskim lupusom

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Abstract

Introduction. Infections in patients with systemic lupus erythematosus (SLE) are a significant factor of morbidity and mortality. Although central nervous system infections, including septic meningitis, are rare in patients with SLE, they can be significant causes of mortality inspite of the prompt and accurate diagnosis and proper management. **Case report.** We presented a woman with the diagnosis of SLE and diffuse proliferative lupus nephritis. Because of disease activity we introduced cytostatic immunosuppressive therapy, cyclophosphamide and then azathioprine. Meningoencephalitis, staphylococcal sepsis and abscess of the brain, with resulting seizures developed. **Conclusion.** This case alerts to the need of careful examination of patients with SLE, collection of adequate cultures and evaluation of predisposition towards ifnections, before the introduction of immunosuppressants due to potentially fatal infection.

Key words:
lupus erythematosus, systemic; central nervous system, infections; meningoencephalitis; immunosuppression.

Apstrakt

Uvod. Infekcije kod bolesnika sa sistemskim eritemskim lupusom (SEL) značajan su faktor morbiditeta i mortaliteta. Mada su infekcije centralnog nervnog sistema uključujući septični meningitis, retke kod bolesnika sa SEL, one mogu biti značajan uzrok mortaliteta i pored brze dijagnoze i adekvatne terapije. **Prikaz bolesnika.** Prikazali smo bolesnicu sa SEL kod koje je došlo do razvoja meningoencefalitisa i apscesa mozga pri pokušaju uvođenja citostatske imunosupresivne terapije ciklofosfamidom, a potom azatioprinom. Kao posledica apscesa ostala je encefalomalacija temporoparijetalnog dela mozga sa posledičnim epi napadima. **Zaključak.** Ovaj slučaj ukazuje na potrebu pažljivog pregleda svakog bolesnika sa SEL, kao i procene sklonosti prema infekcijama pre uvođenja terapije drugim imunosupresivnim agensima (pored glikokortikosteroida), zbog potencijalno fatalnih infekcija koje se kod njih mogu razviti.

Ključne reči:
lupus, eritematozni, sistemski; nervni sistem, centralni, infekcije; meningoencefalitis; imunosupresija.

Introduction

It is known that viral and bacterial infections may be the trigger of development or exacerbation of systemic lupus erythematosus (SLE). The patients with SLE are more prone to infections either due to the nature of disease or the applied immunosuppressive therapy [1]. About 80% of infections in SLE patients are caused by bacteria. Common acute infections in these patients are: pneumonia, urinary infections, cellulitis and sepsis [2]. Of chronic infections, the most frequent is tuberculosis [3], while fungal infections, and those caused by parasites and protozoa are most often opportunistic infections [4–6].

Central nervous system (CNS) infections, including septic meningitis, are rare bacterial complications in SLE, but they can be significant cause of mortality [7]. These infections are most commonly the consequence of a long-term immunosuppressive therapy, and can be a diagnostic problem by mimicking activity of lupus and neurolupus. We presented the instructive and difficult case of CNS infection in a SLE patient.

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Case report

A 33-year-old female patient, has been treated for SLE since 2004. The onset of disease was sudden in March 2004, with edemas, pains and stiffness of joints and febrile condition which was followed by cervical and axillary lymphadenopathy, hepatosplenomegaly and anemia (hematological disease was ruled out on the basis of bone marrow puncture). On admission, bilateral neck and axillary lymph nodes were enlarged, the patient had hepatosplenomegaly. We observed an abscess on the left gluteus.

Laboratory results showed elevated erythrocyte sedimentation rate (ESR 80) and leukocytosis (11.4×10^9/L), anemia [hemoglobin (Hb) 97 g/L] and slight thrombocytopenia (131×10^9/L). Biochemistry was normal (with hypoalbuminemia of 28 g/L). Immunological analyses showed high immunoglobulin G (21.9 g/L), consumption of complements (C3 = 0.43 g/L and C4 < 0.04 g/L), positive antinuclear antibodies (ANA) homogenous 1 : 640, ds DNA ++++, positive anticardiolipin antibodies (ACLA) and positive Coombs test. The urine sediment showed 8–10 fresh, 10–12 pale erythrocytes. Urine culture was negative, 24-hour proteinuria bellow 0.5 g. Gluteal wound swab: *Escherichia coli* X-ray of the heart and lungs and heart ultrasonography showed minor pericardiac effusion.

The patient was diagnosed with SLE on the basis of American College of Rheumatology (ACR) criteria: polyarthralgia, cytopenia, positive ANA, ds DNA, ACLA, pericarditis, and erythrocyturia. The therapy included parenteral glucocorticosteroids (GCS), followed by oral prednisone of 1 mg/kg body weight (bw) in decreasing doses, antibiotics, antiaggregation therapy, H2 blockers. Later, after improving, the patient was on maintenance prednisone dose of 30 mg.

In November 2004, the patient developed the signs of iatrogenic Cushing's syndrome. Due to increase in proteinuria (up to 3.5 g/24 h) and massive erythrocyturia, kidney biopsy was performed and revealed diffuse-proliferative glomerulonephritis with activity and chronicity indexes of 4/24 and 3/12, respectively.

Further treatment included two-time pulse therapy with the intravenous (*iv*) methylprednisolone, 500 mg, followed by pulse therapy of *iv* cyclophosphamide, 800 mg. The patients was advised to take prednisone 20 mg, azathioprine 50 mg, and drugs for gastric mucosal protection.

Eighteen days after *iv* cyclophosphamide pulse therapy, the patient developed massive left-side effusion, hypertension, lower leg edemas, hepatosplenomegaly. During the same evening, the patient's condition worsened, she was febrile (38°C) with a headache. We evacuated 1,400 mL of serous pleural exudation. Proteinuria was 9.39 g/24 h. Parenteral quinolones and cephalosporins were empiricaly introduced in full doses, as well as *iv* methylprednisolone, 3 × 40 mg.

Neurological findings revealed positive meningeal signs without lateralization. Lumbal puncture was performed, and the cerebrospinal fluid was turbid, pouring out under intense pressure. The analysis revealed cerebrospinal fluid (CSF) with 820 cellular elements (98% neutrophils, 2% lymphocytes), hypoglycorrhachia, 1.94 mmol/L, and hyperproteinorrhachia, 1.78 g/L. Etiological examinations of CSF were negative.

The patient was transferred to the Clinic of Infectious Diseases.

Antimicrobial therapy was continued by: ampicilin 3 × 3.0 g *iv*, gentamicin 120 mg, rifampicin 600 mg. After 6 days, isoniazid 300 mg and pirazinamide 1,500 mg were added, because specific CNS infection was suspected. Although antimicrobial and antiedematous therapy was continued, her condition became aggravated, manifested by generalized epileptic seizures. The introduction of antiepileptics (phenobarbiton and carbamazepine) made convulsions stop. Endocranial computed tomography (CT) was carried out and the right temporoparietal hypodense area was evident. At that time, ampicilin was ruled out and vancomycin, 3 × 500 mg, was introduced (in condition of sufficient diuresis), because of cerebritis. Few days later, endocranial magnetic resonance imaging (MRI) demonstrated meningoencephalitis of the right temporo-basic region together with encephalomalacia (Figure 1) and *Staphylococcus aureus* was isolated

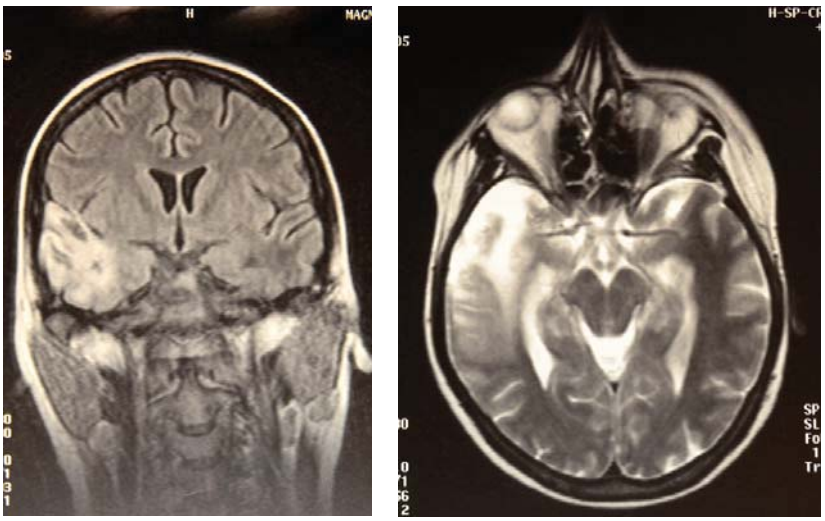

Fig. 1 – Endocranial magnetic resonance imaging meningoencephalitis of the right temporo-basic region together with encephalomalacia.

from two blood cultures. At that time, middle-grade renal failure was registered (creatinine clearance 27.6 mL/min). According to therapeutic algorithm, we introduced meropenem (but in doses of 3 × 1.0 g) with fluconasol. After few days, antituberculotic therapy was excluded. Three weeks later, when the patient's clinical improvement was evident and renal function was repaired (proteinuria 0.89 g/24 h), vancomycin and meropenem were ruled out and antimicrobial therapy was continued with gentamicin 120 mg and cefotaxim 2 × 3.0 g.

Anemia was corrected by the substitution therapy. Control endocranial MRI showed a significant regression of above-described pathological changes but, in further course, agranulocytosis was noted and bone marrow puncture was done. Filgrastim, a colony- stimulating factor, was added, resulting in the retrieval of white blood cell count and afebrile condition. In the meantime, the patient experienced abdominal difficulties, with clinical and radiologic picture of ileus and underwent surgical interventions (laparotomy, ascites evacuation and drainage). Postoperative course was uneventful. Further on, the patient was better, proteinuria was about 1 g/daily. A gluteal abscess developed again, in the right region, and was treated (Figure 2).

In June 2005, worsening of urine sediment and proteinuria occurred, so we introduced mycophenolate-mofetil in increasing doses to 2 g/day. After several days, the patient developed fever and acute bronchitis, followed by nausea, and laboratory inflammatory syndrome. Because of that, mycophenolate therapy was discontinued.

In further course there has been no attempt to introduce immunosuppressive therapy other than GCS. Control endocranial MRI (Figure 3), showed right temporoparietal hypodense area. During the last hospital stay in October 2011, the patient felt mostly well, with occasional events of bronchitis, rare epileptic seizures (approximately 1 per month) and without significant proteinuria.

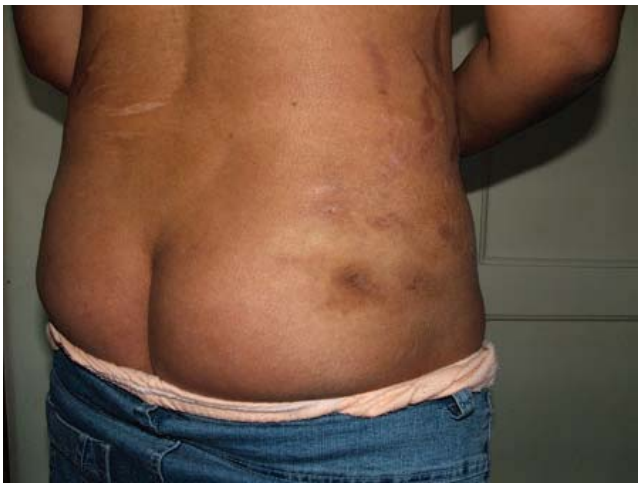

Fig. 2 – An abscess in the right gluteal region.

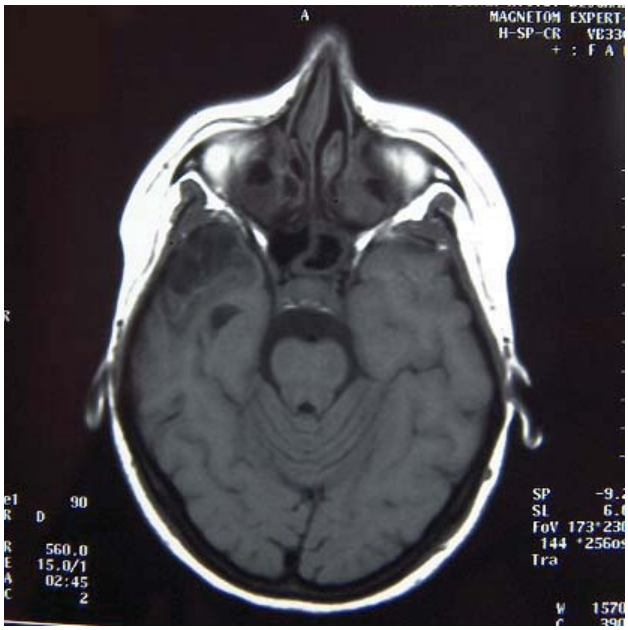

Fig. 3 – Control endocranial magnetic resonance imaging findings: right temporoparietal hypodense area; and chronic sinusitis (opacification of paranasal cavities).

Discussion

One of the most severe complications during SLE condition may be CNS infection, which is most commonly the consequence of a long-term use of GCS and other immunosuppressive agents, as well as immune disorder due to the illness itself. The majority who died from infection were on high dose prednisolone plus at least 1 other immunosuppressive agent and had serologically active disease [8]. CNS infection symptoms may mimic the activity of the disease or, conversely, may be camouflaged by GCS therapy [9].

Reviewing the causes/focus of CNS infection, the possibilities in the presented case were multiple: predisposition to infections due to conditions with complement deficit and reduced bacterial clearance *via* reticuloendothelial system; higher exposure to respiratory infections within her environment (pre-school and school children at home, poor economic conditions); the existing chronic sinusitis (CT-viewed opacification of paranasal cavities) with the possibility of infection spread and the presence of "silent foci" (such as gluteal abscess) which became reactivated upon immunosuppression and could reached the CNS through circulation. In addition, the risk factors of infections described in the literature [10–14] such as: nephritis, activity of the disease, leukopenia, positive dsDNA > 20 IU/mL, prednison in daily dose higher than 10 mg, application of cyclophosphamide, together with hypocomplementemia presenting the independent predictive factor, were all found in our patient.

Due to GCS side effects and the activity of the disease, the presented patient received *iv* pulse cyclophosphamide therapy followed by oral azathioprine [15], which produced many side effects, among them life-threathening CNS infection.

At that time, the question of differential diagnosis was raised: whether it was about SLE exacerbation and development of neurolupus, or even manifestation of antiphospholipid syndrome (APLS), or CNS infection. The following examinations were performed: lumbal puncture, CT scanning and MRI imaging, which confirmed the infection of CNS and ruled out CNS vasculitis and APLS (ACA were, except for the first result, several times negative). We concluded that it was the case of acute neuroinfection in the immunosuppressed patient.

Clinical picture and course of disease with positive blood culture results indicated *Staphylococcus aureus* infection. This is supported by the fact that epileptic seizures first occurred during meningoencephalitis and occasionally kept on appearing as the consequence of encephalomalacia.

The patient's condition demanded antibiotic therapy from the beginning. After neuroradiologic diagnostics and positive blood culture, anticerebritic therapy was necessary: combination of the third generation cephalosporines with vancomycin, and consenquently, the combination of meropenem and vancomycin were used [16, 17]. From the beginning, the patient was on full-dose antibiotic therapy. At the moment of decission about meropenem dosage, we were guided by the two facts: the patient had middle-stage renal failure, and meningoencephalitis had already achieved clinical improvement, so the dose of meropenem was adapted (from the recommended dose of 3×2.0 g to 3×1.0 g).

We consider this report instructive and interesting because of many aspects. CNS infections are rare in patients with SLE, but they can be significant causes of mortality. Kim et al. [7] found 1,420 Korean patients with SLE out of whom 20 (1.4%) had meningitis.

During a 20-year review period, among 3,165 Taiwanese SLE patients, Hung et al. [18] identified 17 patients with CNS infections. *Cryptoccocus neoformans* was the causative microorganism in 10 patients and bacterial meningitis was found in 7 of then. Most patients (94%) had active SLE at the time of CNS infection. A total of 15 patients received corticosteroid therapy, and of these, 7 in combination with immunosuppressive agents. The mortality rate was extremely high (41.2%) [18]. The presented patient also had active SLE at the time of infection, and received GCS therapy in conjunction with immunosuppressive agents.

Yang et al. [19] described 38 SLE patients with CNS infections (*Mycobacterium tuberculosis* was identified in 19 of the patients, *Listeria monocytogenes* in 3, *Klebsiella pneumoniae* in 1, *Staphylococcus aureus* in 1, *Cryptococcus neoformans* in 12 patients, and *Aspergillus fumigatus* in 1 patient).

In 2009, Baizabal-Carvallo et al. [20] reported 23 patients with SLE and meningitis among 1,411 SLE patients in Mexico.

Conclusion

Since SLE patients are at higher risk of infections, before utilization of any immunosuppressive therapy, it is necessary to identify infections. Complete and careful examination of a patient, collection of throat, nasal and sputum swabs, urine culture as well as monitoring of CNS manifestations are required for choosing the therapy. Also, care is required about additional risk factors (mentioned above), and individial disposibility for infection, and to be aware that infection in immunosuppressed patients can be unpredictible.

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