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Review Article

Systemic Lupus Erythematosus Complicated by Macrophage Activation Syndrome and Pancreatitis

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Abstract

Systemic lupus erythematosus is the most common systemic pediatric disease. It affects especially the big girls in the peripubertal period. Complications such as lupus nephropathy and haemophagocytosis are well known, whereas an association with acute pancreatitis is rare. The purpose of this work is to describe this association in our context. We report the case of a 14-year-old girl hospitalized for abdominal pain with a history of first degree consanguinity, lupus nephropathy diagnosed 11 months before treated with prednisone, hydroxychloroquine sulfate and Mofetil mycophenolate with poor compliance, and two episodes of acute pyelonephritis treated with antibiotic. The clinical examination revealed an alteration of the general state and febrile polyarthritis. Biological examinations showed bicytopenia (lymphopenia at 950 / mm3, arterenative anemia at 9.8 g / dl hemoglobin), a biological inflammatory syndrome (95 mm / hr SDR, CRP 8.6 mg / l), a hyponatremic (Na + at 113 mEq / l), an alkaline reserve at 14 mEq / l, hepatic cytolysis (ASAT at 160 IU / l, ALAT at 72 IU / l), macrophage activation stigmas (triglycerides 2.69 g / l, ferritinemia at 3986 mg / l) confirmed in the medullogram by the demonstration of haemophagocytosis, signs of tissue pain (LDH at 1419 IU / l, CK at 2627 IU / l), a 24-hour proteinuria positive at 61 mg / kg / day with preserved renal function and acute pancreatitis (lipase at 351 IU / l). The patient was put into digestive rest with continued prednisone and adjuvant adjunctive therapy, Hydroxychloroquine sulfate and Mofetil mycophenolate (not followed). The evolution had been marked by the aggravation of its state resulting in the death 48 hours later. The age of early onset of the disease, renal involvement, haemophagocytosis, acute pancreatitis and non-adherence are all pejorative factors that have reduced its prognosis.

Keywords: Haemophagocytosis; Lupus Nephropathy; Macrophage Activation Syndrome; Pancreatitis; Systemic Lupus Erythematosus

Introduction

Systemic lupus erythematosus is a systemic disease, autoimmune, chronic with highly polymorphic visceral manifestations and unpredictable prognosis. In 15 to 20% of the cases, the disease will begin before the age of 16 and will be classified in the juvenile category [1] which is marked by a succession of relapses accompanied by an alteration of the general state and periods of remission. Complications such as lupus nephropathy or macrophage activation syndrome are well known while rare and exceptional acute pancreatitis can lead to its discovery [2,3]. On the other hand, the association of these complications during a lupus flare had not yet been reported in pediatrics. There is no curative treatment, but new therapeutic perspectives are nevertheless being studied [4]. The purpose of this work is to describe this association in our context.

Observation

This is a 14-year-old girl who was hospitalized for abdominal pain. She came from a 1st degree consanguinous marriage and was followed for a severe period of 11 months. The diagnosis of juvenile systemic lupus erythematosus was selected according to the American College of Rheumatology (ACR 1982) classification revised in 1997 and adapted to the child by the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria, which are more sensitive and constitute the essential tool for diagnosis in children [5-7]. In fact, she presented: malar erythema in butterfly wings, oral aphtosis, synovitis of proximal interphalangeal joints, cervical spine involvement, positive direct coombs test, discrepancy between biological inflammatory syndrome (VS = 57 mm)

in the first hour, microcytic anemia at 11 g / dl) and (lymphopenia at 900 elements / mm 3, thrombocytopenia at 124 000 elements / mm^3), a collapsed complement (C3 = 0.51 mg / l, C4 = 0.07 mg / l, CH 50 = 24.3 mg / l), antinuclear antibodies positive, anti-sm antibody search, anti sm / rnp, anti v1rnp, anti ssa / ro60kd, anti j0-1, anti scl-70, anti-ribosome, anti pm-scl 100, anti-ku, anti-cenp, anti-pcna and anti-native DNA were negative, 24-hour proteinuria positive at 15 mg / kg / day, class III proliferative proliferative glomerulonephritis lesions with activity index = 15 and chronicity index ≤ 10. The evolution was favorable under prednisone (2 mg / kg / day for a weight of 47 kg followed by a progressive decrease to 20 mg / day) associated with adjuvant treatment and hydroxychloroquine sulfate (200 mg / day). Seven months after the discovery of the disease, she was hospitalized for acute pyelonephritis to *Salmonella* spp. with 24-hour proteinuria at 53.33 g / kg / day. The indication for selective immunosuppressive therapy was raised, prompting the prescription of Mofetil mycophenolate (1500 mg / day in three divided doses) not followed by the patient. The evolution of acute pyelonephritis was favorable with Ceftriaxone and Gentamycin intravenously.

Four months later, she was readmitted for abdominal pain. During the interrogation, she had been complaining for three weeks, of a fever at 38°C-39°C, of anorexia, asthenia and uncalculated weight loss; polyarthralgia (large joints) responsible for prolonged bed rest, abdominal pain and a cessation of materials and gas for 2 days. On examination, she weighed 42 kg, was feverish at 39°C, had polyarthritis with irreducible flexum of both knees and wrists, a limitation of mouth opening associated with aphtosis and thrush, amyotrophy of limbs. The abdomen was sensitive only at the epigastric level. She also had a lazy dehydration crease, a superinfected sacroiliac eschar, and a delayed onset of secondary sex characteristics classified as Tanner II. There was no hepatomegaly, splenomegaly, or lymphadenopathy. Biological examinations showed bicytopenia (leukocytosis at 10290 / mm^3 with lymphopenia at 950 / mm^3, normochromic normocytic anemia at 9.8 g / dl hemoglobin and arteregenerative at reticulocyte level at 52000 / mm^3, platelets normal at 356000 / mm^3), a biological inflammatory syndrome (95 mm / hr SDR, CRP 8.6 mg / l), hyponatremic dehydration (Na + at 113 mEq / l) with metabolic acidosis (alkaline reserve at 14 mEq / l), hepatic cytolysis (ASAT 160 UI / l, ALT at 72 IU / l) with normal bilirubin, macrophage activation stigmas (triglycerides 2.69 g / l, ferritinemia at 3986 mg / l) confirmed in the medullogram by evidence of haemophagocytosis, stigmata Tissue pain (LDH at 1419 IU / l, CK at 2627 IU / l), a 24-hour proteinuria positive at 61 mg / kg / day. In addition, ECBU was positive at *E. coli*. Renal function was maintained, calcemia, complement (C3, C4, CH50) and normal crase balance, blood cultures, and serology (of hepatitis A, B, and C, Epstein-Barr virus , cytomegalovirus and syphilis) negative. The persistence of epigastric pain had motivated the achievement of a pancreatic assessment which had returned to favor of an acute pancreatitis with a lipase at 351 UI / l (normal <78 IU / l) thus giving the indication of a scanner abdominal showing a normal sized pancreas with no detectable focal lesions, bilateral cortico-renal cysts and micro-calcifications, and calcifications of the soft tissues of the coxofemoral joints.

In view of this clinical picture, the diagnosis of systemic lupus erythematosus complicated by macrophage activation syndrome and pancreatitis was made. The patient had benefited at the same time from the resting of the digestive tract, the correction of intravenous hydroelectrolytic disorders, treatment of acute pyelonephritis with Ceftriaxone associated with Gentamycin, analgesic, oral care (by Miconazole oral gel), pressure ulcer care, continuation of Hydroxychloroquine sulfate (200 mg / day) and Prednisone (15 mg / day). The evolution had been marked by the aggravation of the state Clinical condition characterized by a general state and impaired consciousness with Glasgow score at 11/15, epigastric pain and persistent fever, all biologically confirmed by an increase in lipase at 405 IU / l and ferritinemia at 6685 mg resulting in the death of patient 48 later.

Discussion

Juvenile systemic lupus erythematosus is the most common systemic disease in pediatrics. Female dominance is constant at any age with a juvenile ratio of around 4.6 / 1 [1]. Complications such as lupus nephropathy or macrophage activation syndrome are well known while acute pancreatitis is rare and exceptional. Thus, the clinical and biological characteristics of our patient would join those found globally in the literature (cutaneous and articular involvement) if she had not developed the severe form of the disease that simultaneously associated these three complications. Indeed, this association, during a lupus flare, had not yet been reported in pediatrics. With regard to the lupus nephropathy, it is the most frequent; in two Arab series, it accounts respectively for 63.3% and 80% of renal cases [8]. As for macrophage activation syndrome, it is reputed to complicate certain autoimmune diseases, including the systemic lupus erythematosus, is rather rare in juvenile lupus with a prevalence of 0.9 to 4.6% [9]. It could be attributable to the major inflammatory context, especially since it is revealing 5 times out of 6, in patients who are free from any medication [10,11]. It is difficult to diagnose lupus due to clinico-biological similarities. Except for the presence of haemophagocytes on the myelogram which signs its formal diagnosis, to date, the only discriminative examination is the increase in ferritinemia at levels exceeding 500 g / L with a specificity of 93% and a sensitivity of 100% [9,10]. This dosage is most valuable in the absence of hemophagocytes on the myelogram. Acute pancreatitis, reported in 4.2% of juvenile series, is considered by some authors as a marker of severity of outcome often fatal, by others as of iatrogenic origin or a manifestation of macrophage activation syndrome [12-14]. Our patient had not survived.

The therapeutic management of severe forms of juvenile systemic lupus erythematosus is based on the use of methylprednisolone infusions at a dose of 1 g / 1.73 m^2. They are also indicated in cases of macrophage activation and / or acute pancreatitis if the cause of pancreatitis has been associated with lupus [2,15]. However, our patient could not benefit because being on long-term corticosteroid therapy, the cause of pancreatitis could be attributed to iatrogeny related to Prednisone, or lupus. Immunosuppressive drugs are unavoidable in cases of severe renal impairment, central nervous system or haematological rebellious, but there are no validated recommendations on their exact indications in pediatrics. Nevertheless, their addition is common practice in advanced forms of lupus nephropathy. Although Cyclophosphamide is the most prescribed molecule in this indication, the fact remains that it retains a high level of toxicity that has gradually led to its replacement by Micophenolate mophetyl, whose efficacy no doubt with a much better tolerance [16]. Treated with hydroxychloroquine sulfate orally, the high cost of Micophenolate mophetyl did not allow the optimal management of our patient. Other products such as azathioprine have been tried in the consolidation phase with satisfactory results [17]. The prescription of rituximab finds its place in aggressive forms including hematologic that do not respond to first-line treatments, but also specifically in certain refractory forms of lupus nephropathy allowing a significant decrease in doses of corticosteroids [18]. Antiproteinurics in turn hold a privileged place in the persistent proteinuria that does not meet the treatments required. Many authors report that the age of early onset impacts the clinical expression of the disease and confers a more severe prognosis [19]. On the other hand, renal and neurological disorders are unanimously accepted in terms of unpleasant evolution [20], as in our case, who died 11 months after the discovery of severe lupus nephropathy class III, poorly controlled by prednisone, hydroxychloroquine sulfate and a lack of treatment with mophophenolate mophetyl.

Conclusion

Systemic lupus erythematosus is the most common systemic pediatric disease. It is of multifactorial origin and its exact etiology remains unknown. Complications such as lupus nephropathy and macrophage activation syndrome are well known, whereas an association with acute pancreatitis has not yet been described in pediatrics. The age of early onset of the disease, renal involvement, macrophage activation, acute pancreatitis and non-adherence are all negative factors that have been life-threatening for our patient.

Conflict of interest

The authors declare that they have no Conflict of interest.

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