A Four Year Old with Multisystem Autoimmune Disorder: Systemic Lupus Erythematosus, a Third World Prodigy

Summary

Childhood-onset Systemic Lupus Erythematosus (SLE) has an incidence of 0.3-0.9/100,000 children. It is very rare to find a case of childhood-onset SLE before 5 years of age. We describe a case of a 4-year-old female child, from a low-socioeconomic background who was diagnosed with SLE based on a typical rash, oral ulcer, positive laboratory parameters such as ANA, anti-ds DNA, anti-nucleosome, anti-histone antibodies, and positive lupus anticoagulants. There was an involvement of each system with considerable signs and symptoms including lupus nephritis, a cardiological complication such as Libman-Sack endocarditis, and neurological manifestations showing diffuse cerebral atrophy. The child was also positive for parameters linking to the presence of Macrophage Activation Syndrome MAS). The hypercoagulable state of SLE has been linked to more central nervous system involvement, cardiovascular dysfunction, renal complication, and hyponatremia as indicated in our case making it more riveting.

Introduction

Systemic Lupus Erythematosus is a chronic autoimmune disease characterized by autoantibodies production directed against anti-nuclear antibodies (ANA). Other types of antibodies include anti-Smith and anti-dsDNA [1]. The disease has a predilection for women, especially in the child-bearing age [2], but can essentially occur at any age. It generally affects multiple organs such as the brain, heart, lung, kidneys, gastrointestinal tract, and the skin where it has a typical manifestation. Diagnosis is based on clinical examination and elevation of certain laboratory measures. A suitable diagnosis can be based on the levels of ANA, CRP, complement proteins, and ESR [3]. C-reactive protein can not be used to establish a diagnosis of SLE, although it can be useful for the differential diagnosis of Rheumatoid arthritis (RA) and SLE [4]

Childhood-onset SLE occurs in patients below 18 years of age and has been described to have an incidence of 0.3-0.9/100,000 children [5]. However, based on the age of onset, neurologic, renal, hematologic manifestations are more commonly seen in juvenile SLE, while in adult-onset SLE the disease can be more aggressive [6]. What we describe here is a case of a juvenile SLE in a child with typical involvement of kidneys, heart and positive markers for Macrophage activation syndrome (MAS). Later is a type of hyperinflammatory syndrome and a type of hemophagocytic lymphohistiocytosis (HLH), recognized by having at least 5 out of 8 criteria in patients, including pancytopenia, hypofibrinogenemia, hypertriglyceridemia, and hyperferritinemia, etc [7]. MAS has a 0.9–4.6% incidence with SLE [7].

Case presentation

A four-year-old female from a low socioeconomic background was admitted with complaints of facial rash for over one month and intermittent, fever, generalized weakness, and ataxia for three months. The rash was non-blanching, palpable, non-itchy, and found over the face (Figure1), palms, and soles of feet (Figure 2). It was a classic malar rash spanning across cheeks and nasal bridge. Her torso was also covered with a maculopapular rash (Figure 3), non-blanching, and appeared as small red confluent papules. The rash was coupled with vasculitis over palms and soles and a red inflamed tongue. The child had difficulty in standing and walking. In her previous admissions, the patient was only treated symptomatically with antibiotics, antihistamine drugs, and various creams for local applications for four months prior to a diagnosis. She had eventually undergone relevant laboratory investigations and was diagnosed with Systemic Lupus Erythematosus. However, on recent admission, the patient had aggravated symptoms with persistent generalized weakness and was unable to stand unassisted. Additionally, her rash had spread all over her body with swelling and bruising of the right arm and cellulitis in the adjacent arm. Oral ulcers were also noted. She also developed aphasia and showed behavioral changes.

Figure 1: shows a malar, non-itching and non-blanching, on the cheeks of the patient

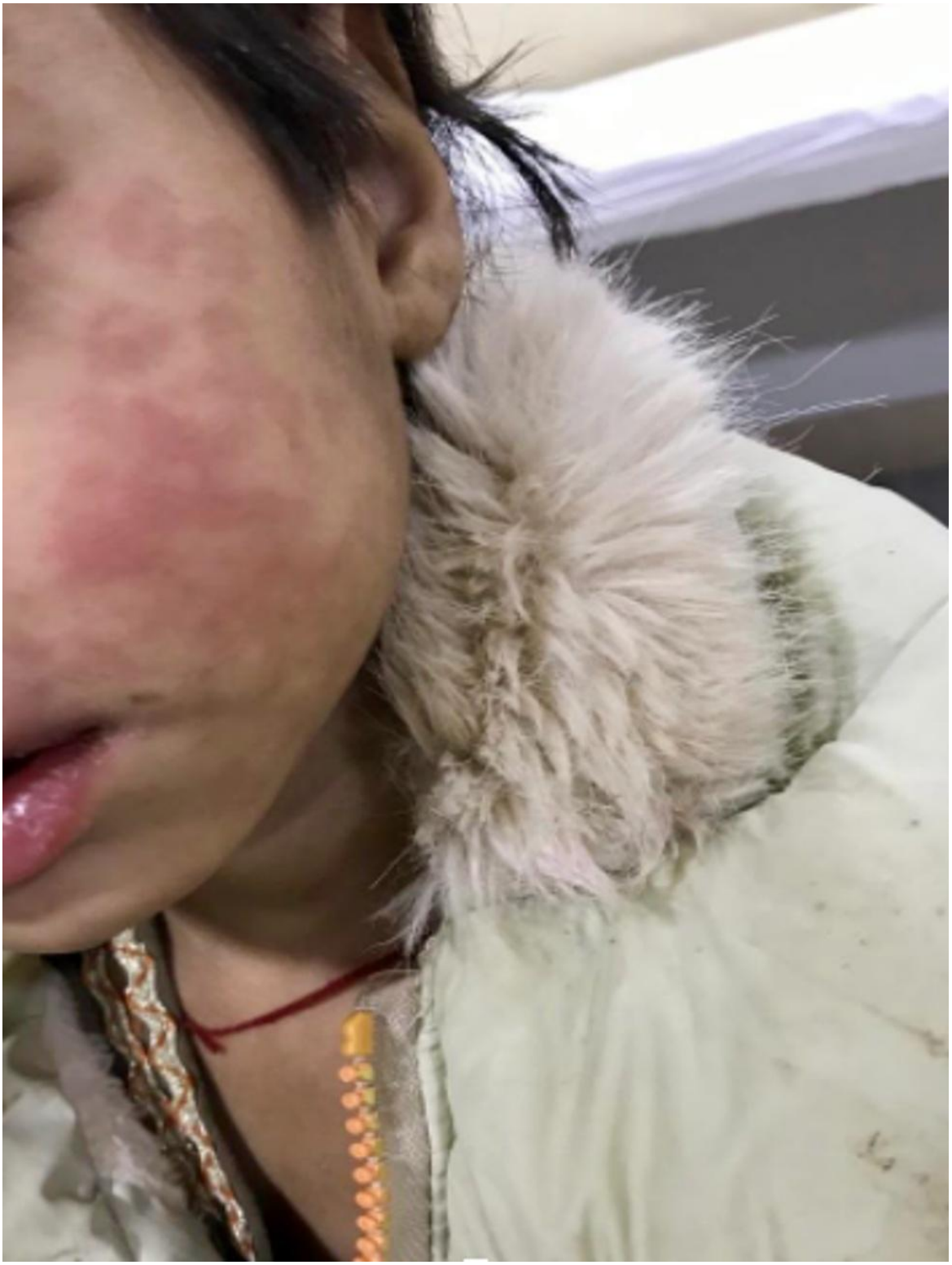
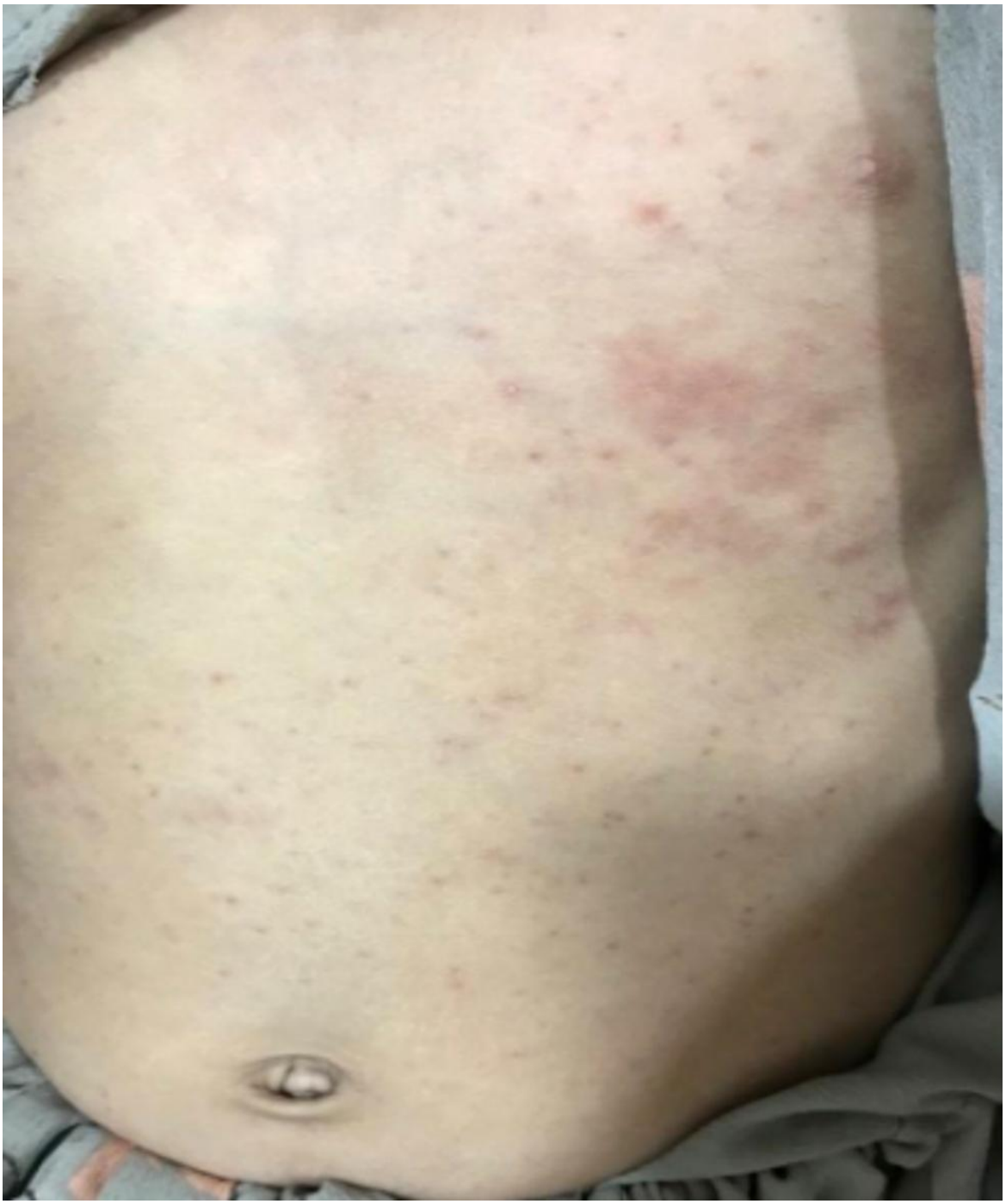


Figure 2: shows an erythematous rash on the palms of the patient

Figure 3: shows a maculopapular rash on the abdomen of the patient



Her SLE diagnosis was made with a lupus-specific antibody profile, showing ANA to be positive with a homogeneous pattern. Anti-dsDNA was 8.43 U/ml. The ENA profile showed positive anti-nucleosomes ++ and anti-histone + autoantibodies. Her worsened rash had caused concerns for an active lupus flare and possibly an infection, her beta 1,3-β-d-glucan (BG) assay screened for an invasive fungal infection was negative. There were significantly raised IgG levels 3012 mg/dl (504-1464 mg/dl), IgM levels 516 mg/dl (24-210 mg/dl) IgA levels of 254 mg/dl (27-195

mg/dl) and IgE 245 I.U./ml (20 to 100 I.U./ml). This was suggestive of systemic lupus erythematosus glomerulonephritis. Furthermore, urinalysis showed protein (189.30mg/dl) and urine creatinine (63.41mg/dl), positive albumin, leukocytes, epithelial cells (10), and mucus. Her complement proteins were also remarkably low, with C3 at 18.6 mg/dl (90-180 mg/dl) and C4 at 2.5 mg/dl (10-40 mg/dl). Renal biopsy finally showed grade IV nephritis. In addition to supportive care, she was treated with oral steroids and hydroxychloroquine sulfate for her lupus. Patients responded significantly well to the administration of steroids with reduction in inflammatory manifestations of SLE. After discovery of renal involvement, low dose Methylprednisolone pulse was given for 5 days and pulse intravenous cyclophosphamide (IVC) for one day when her condition had worsened in the ICU

High triglyceride (204 mg/dl) and high LDH (1873 U/L), and ferritin (519 ng/ml), along with fever and cytopenia raised suspicion for Macrophage Activation Syndrome (MAS), although her fibrinogen was normal at 322.9 mg/dl. The MAS parameters were kept in check.

On recent admission, a detailed echocardiogram was performed showing repeated vegetation particularly on the mitral valve including thrombosis and fibrinous material indicative of Libman-Sack endocarditis. Correspondingly the cardiology department ordered four blood cultures at different time intervals to confirm the pathology. All the blood cultures were sterile, moving the evidence more in the favour of Non-Bacterial Thrombotic Endocarditis (NBTE), a characteristic cardiac manifestation of an autoimmune disease like SLE. A significant correlation exists between LS endocarditis and SLE duration and severity. The child was administered aspirin as well as clexane to prevent any thromboembolic event. Echocardiograms were repeated which showed no significant vegetation.

During her stay, the child acquired abdominal pain coupled with left hypochondrial tenderness. A CT Scan of the abdomen was conducted showcasing wedge-shaped hypodensity in the Spleen. Since hypercoagulable disorders directly lead to a significant percentage of thrombosis it was a definitive indication for splenic vein thrombosis, making our case furthermore interesting.

Due to neuropsychiatric symptoms, an MRI of the brain was done that showed ventricular dilatation with prominent sulci, representing diffuse cerebral atrophy. The patient's lupus anticoagulants test was positive. Bone Marrow biopsy was inconclusive. Skin biopsy was taken and on histopathological examination, there was no discrete nodule, discoloration, or lesion with an unremarkable epidermis. There was no collection of Langerhans cells seen, thereby ruling out Langerhans cell histiocytosis. There was a negative indication for CD1a with no evidence for a granuloma or malignancy.

The patient had severe anemia with a Hemoglobin of 7.3 g/dl. In addition, the blood film was suggestive of microcytosis, anisocytosis and showed polychromasia, target cells, hypochromic red blood cells, and teardrop cells. Her Coombs test was negative and her reticulocyte count was 0.1 %, ruling out autoimmune hemolytic anemia. Her total White blood cell (WBC) count was 12x109/L.The differential count of white blood cells with neutrophils and reactive

lymphocytes that were spotted. She had thrombocytopenia with her platelet count at 120x109/L. Her inflammatory profile showed C-Reactive Protein (CRP) to be at 39 mg/dl and ESR at 97 mm.

Our patient's condition prevailed and manifested as a result of genetic predisposition and was not a result of drug reaction or exposure to chemicals. Due to its deep rooted causes, it led to the deterioration of patients' condition with a multi systemic manifestation resulting in endless complications. An earlier diagnosis with prompt management and drug administration, the condition was stabilized with a possibility of a good prognosis.

Discussion

SLE is an autoimmune disorder characterized by autoantibody production causing inflammation in various organs. Our case was of a juvenile SLE in a four-year-old Asian girl, presenting with classical symptoms of the disease. Childhood SLE usually has an onset at 11-12 years and is common in Asians [5]. However, it is rare to find a case under five years of age [8]. Similar cutaneous involvement was seen in another case of juvenile SLE, with erythematous, non-blanching, and a macular rash over the body [9]. The rash is seen in 60 - 85% of children and has a typical pattern as seen over the nasal bridge [5]. Although the child had developed cutaneous symptoms after the initial administration of Cephalosporin antibiotic, the symptoms did not abate after cessation of the drug. Drug-induced SLE usually happens after years of exposure, rarely involving the CNS and kidneys [10].

Raised levels of Anti-dsDNA antibodies are important for the diagnosis of SLE, included in the American College of Rheumatology classification criteria [5]. Patients mostly have raised levels of the IgG class of antibodies, while 30% develop antibodies of IgA class [11]. In this case, there was hypergammaglobulinemia with raised IgG, IgM, and IgA. A cross-sectional study on 83 patients with lupus nephritis found polyclonal hypergammaglobulinemia with high IgG in 15% of the patients [12]. At the same time, IgM has been reported to have a negative association with nephritis ($P< 0.0001$) (9). This could explain the IgG/IgM ratio which is used to determine renal involvement in SLE. A ratio > 0.8 is associated with renal involvement as reported by Förger et al.[13], however, Villalta et al. reported a higher ratio of > 2.09 [14]. Nevertheless, our ratio was higher than both, indicating a potential renal involvement, indicated by our patient’s renal biopsy. Renal and neuropsychiatric involvement have been commonly associated with Juvenile SLE cases [8].

With regards to the disease progression and severity, inferences can be drawn from the clinical symptoms and complement component levels. The presence of butterfly rash and the spread of our patient’s rash showed disease progression as opposed to only finding fever and fatigue, which is seen in the early stages of the disease [4]. Her low complement levels of C3 and C4 could not be attributed to any other underlying liver disease or protein-losing enteropathy. The lower levels of complement seen in SLE can be attributed to their consumption during lupus flares and the impairment in the clearance of apoptotic cells and immune complexes formed between antibodies and antigens [15]. To describe lupus renal flares with complement levels, one study associated low C4 with a two-month pre-flare period, and C3 independently with flare visit [3].

Our patient only fulfilled four out of 8 criteria for MAS, including fever, cytopenia, hypertriglyceridemia, and elevated LDH. MAS, previously described in association with juvenile idiopathic arthritis (JIA), can also concomitantly occur with SLE. According to one study, MAS associated with SLE caused more CNS involvement ($p < 0.001$) and hyponatremia (exact $p = 0.005$), and required more mechanical ventilation ($p = 0.003$), and had more cardiovascular dysfunction ($p = 0.02$) than in patients with MAS and JIA [16]. However, there was no cardiac dysfunction in our patient. The probable MAS, in this case, was secondary to autoimmune SLE, therefore, classified as secondary HLH [17]. One study found ferritin levels of >662.5 ng/mL and LDH levels of >359 U/mL to be optimal for predicting the co-occurrence of MAS in SLE [18]. Treatment of MAS involves mostly corticosteroids, but in the case of steroid resistance, IL-1 antagonists such as anakinra and intravenous immunoglobulin can also be used [17]. Our patient responded well to steroid treatment.

Hydroxychloroquine is a very common drug choice that is used to prevent disease flare-ups and manage minor symptoms such as arthralgia, fatigue, fever, and rash. Other treatment options include synthetic drugs such as glucocorticoids, cyclophosphamide, azathioprine, and mycophenolate. Biological agents are also used for treatment such as belimumab and intravenous immunoglobulins [19]. Cyclophosphamide therapy is usually reserved for patients non-compliant to oral medications and neuropsychiatric systemic lupus erythematosus because of the risk of serious toxicities [5].
Hence with a prompt diagnostic approach and adequate administration of drugs such as hydroxychloroquine, patient is rewarded a better prognosis with decreased severity of symptoms and a timely control on disease progression.

Conclusion:
In conclusion, chronic multisystem autoimmune systemic lupus erythematosus especially at a young age is a very rare entity with its many complicated manifestations. Our report on a four-year old asian girl might be the first time in literature to present such aggravated signs and symptoms targeting each organ system of the body. Particularly associated with the presence of autoantibodies against the body's own tissue with complications including lupus nephritis, a cardiological complication such as Libman-Sack endocarditis, and neurological manifestations showing diffuse cerebral atrophy. This case report reinforces the significance of a rigorous follow-up in children and adolescents with autoimmune disorders especially in regards to disease progression and severity to promote a better prognosis and longevity of life.

Highlights

- SLE can present at any age. Childhood-onset SLE represents 15 to 20 percent of all SLE patients, affecting about ten out of one million children per year.
- Patients with suspicion of a systemic condition must be investigated thoroughly to avoid complications.

- Due to the prevalence of infectious diseases, it's a challenge to diagnose conditions like SLE in developing countries such as Pakistan.
- Due to poor background and gender discrimination, women are often neglected and suffer at the hands of inequality.

Declarations

The authors declare that they have no competing interests

The guardians consent to the information being shared in the manuscript

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As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors

References

1. Yong PFK, Aslam L, Karim MY, Khamashta MA: Management of hypogammaglobulinaemia occurring in patients with systemic lupus erythematosus. Rheumatology. 2008, 47:1400–5. 10.1093/rheumatology/ken255

2. Website. Accessed: July 10, 2021. Lupus Basics. 2018. https://www.cdc.gov/lupus/basics/index.html.

3. Birmingham DJ, Irshaid F, Nagaraja HN, et al.: The complex nature of serum C3 and C4 as biomarkers of lupus renal flare. Lupus. 2010, 19:1272–80. 10.1177/0961203310371154

4. Li W, Li H, Song W, et al.: Differential diagnosis of systemic lupus erythematosus and rheumatoid arthritis with complements C3 and C4 and C-reactive protein. Exp Ther Med. 2013, 6:1271–6.
5. Levy DM, Kamphuis S: Systemic Lupus Erythematosus in Children and Adolescents. Pediatric Clinics of North America. 2012, 59:345–64. 10.1016/j.pcl.2012.03.007
6. Tucker LB, Uribe AG, Fernández M, et al.: Adolescent onset of lupus results in more aggressive disease and worse outcomes: results of a nested matched case–control study within LUMINA, a multiethnic US cohort (LUMINA LVII). Lupus. 2008, 17:314–22. 10.1177/0961203307087875
7. Granata G, Didona D, Stifano G, Feola A, Granata M: Macrophage Activation Syndrome as Onset of Systemic Lupus Erythematosus: A Case Report and a Review of the Literature. Case Reports in Medicine. 2015, 2015:1–4. 10.1155/2015/294041
8. Gheith RE, El-Gazzar II, El Fishawy HS, Nour El-Din AM, Bahgat DMR, Gheita TA: Juvenile and juvenile-onset systemic lupus erythematosus patients: Clinical characteristics, disease activity and damage. Egyptian Pediatric Association Gazette. 2017, 65:49–53. 10.1016/j.epag.2017.03.003
9. Jaybhaye AP, Sutay NR, Chate SV, Rathod TN: Juvenile systemic lupus erythematosus: A diagnostic dilemma. J Nat Sci Biol Med. 2011, 2:229–31.
10. Vedove CD, Del Giglio M, Schena D, Girolomoni G: Drug-induced lupus erythematosus. Archives of Dermatological Research. 2009, 301:99–105. 10.1007/s00403-008-0895-5
11. Witte T, Hartung K, Sachse C, et al.: IgM anti-dsDNA antibodies in systemic lupus erythematosus: negative association with nephritis. Rheumatology International. 1998, 18:85–91. 10.1007/s002960050063
12. Cuadrado MJ, Calatayud I, Urquizu-Padilla M, Wijetilleka S, Kiani-Alikhan S, Karim MY: Immunoglobulin abnormalities are frequent in patients with lupus nephritis. BMC Rheumatology. 2019, 3.: 10.1186/s41927-019-0079-2
13. Förger F, Matthias T, Oppermann M, Becker H, Helmke K: Clinical significance of anti-dsDNA antibody isotypes: IgG/IgM ratio of anti-dsDNA antibodies as a prognostic marker for lupus nephritis. Lupus. 2004, 13.: 10.1191/0961203304lu485oa
14. Villalta D, Bizzaro N, Bassi N, et al.: Anti-dsDNA antibody isotypes in systemic lupus erythematosus: IgA in addition to IgG anti-dsDNA help to identify glomerulonephritis and active disease. PLoS One. 2013, 8:e71458.
15. Raj N, Waters B: Can Cell Bound Complement Activation Products Predict Inherited Complement Deficiency in Systemic Lupus Erythematosus? Case Reports in Rheumatology. 2016, 2016:1–4. 10.1155/2016/8219317
16. Bennett TD, Fluchel M, Hersh AO, et al.: Macrophage activation syndrome in children with systemic lupus erythematosus and children with juvenile idiopathic arthritis. Arthritis Rheum. 2012, 64:4135–42.
17. Sandler RD, Tattersall RS, Schoemans H, et al.: Diagnosis and Management of Secondary HLH/MAS Following HSCT and CAR-T Cell Therapy in Adults; A Review of the Literature and a Survey of Practice Within EBMT Centres on Behalf of the Autoimmune Diseases Working Party (ADWP) and Transplant Complications Working Party (TCWP). Front Immunol. 2020, 11.: 10.3389/fimmu.2020.00524

18. Liu A-C, Yang Y, Li M-T, et al.: Macrophage activation syndrome in systemic lupus erythematosus: a multicenter, case-control study in China. Clinical Rheumatology. 2018, 37:93–100. 10.1007/s10067-017-3625-6
19. Ponticelli C, Moroni G: Hydroxychloroquine in systemic lupus erythematosus (SLE). Expert Opin Drug Saf. 2017, 16.: 10.1080/14740338.2017.1269168

Legends

Picture 1: Malar rash, also named a butterfly rash, is a common facial presentation of SLE. It is characterized by an erythematous flat or raised rash across the bridge of the nose and cheeks, which usually spares nasolabial folds.

Picture 2: red spots or a scaly, purple rash on various parts of the body, including hands. Especially occurs in areas exposed to sun

Picture 3: Generalised maculopapular rash over torso. This rash is flat, red, and itchy, and it usually appears after sun exposure.