A Teenager With Rash and Fever: Juvenile Systemic Lupus Erythematosus or Kawasaki Disease?

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INTRODUCTION

Kawasaki disease (KD) and systemic lupus erythematosus (SLE) are immune mediated diseases characterized by varied clinical features that may include vasculitis (1–3). Vasculitis in lupus is most commonly due to the local deposition of immune complexes, but some patients have an inflammatory vasculopathy in the absence of local immune complex deposition (3). SLE can present coronary arteritis with aneurysm formation (4). We present three patients with overlapping...
features of KD and SLE. All patients and/or parents provided informed consent for publication of the cases.

Case 1
A 16-year-old male presented with a history of fever, weakness, headache with photophobia, abdominal pain, vomiting, and axillary lymphadenopathy. On physical examination he had persistent fever, conjunctival injection, malar erythema, erythematous and cracked lips, bilateral parotid enlargement, cervical lymphadenopathy and a diffuse photosensitive rash. Sicca symptoms were not present. KD was diagnosed, and intravenous immunoglobulins were started at 2 g/kg in addition to aspirin. The echocardiogram was within normal limits. After treatment, he was afebrile for 24 h, after which he presented seizures and neurological deterioration. Cranial computed tomography revealed changes suggestive of aseptic meningitis. A skin biopsy demonstrated an atrophic epidermis, necrotic keratinocytes, hydropic degeneration of the basal layer, basal membrane thickening and periadnexal and perivascular lymphocytic infiltration. Anti-Ro and IgM anti-β2-glycoprotein-1 antibodies were positive, antinuclear antibodies were negative. The diagnosis of systemic lupus erythematosus was made based on the presence of seizures, malar rash, photosensitivity and, positive anti-β2-glycoprotein-1 and anti-Ro antibodies. Corticosteroids, hydroxychloroquine, and methotrexate were started. He has been followed for more than 2 years, and the corticosteroids have been tapered with good evolution.

Case 2
A 12-year-old male was transferred to our hospital with the diagnosis of lupus. He had a history of 20 days of fever, arthralgias, alopecia, a thoracic and abdominal rash, vomiting, oral ulcers, pleural effusion, pancytopenia, lymphopenia, and positive antinuclear antibodies (1:320). On physical examination the patient had palmpoplantar erythema with desquamation and perineal erythema. Work-up showed a complete blood cell count within normal limits.

Abbreviations: KD, Kawasaki disease; SLE, systemic lupus erythematosus; IVIG, intravenous immunoglobulins; AST-Aspartate aminotransferase, ALT-Alanine transaminase.
TABLE 2 | Definitions of SLE classification criteria.

| ACR 1997 | SLICC 2012 | EULAR/ACR 2019 |
|----------|------------|----------------|
| **Clinical criteria** | | |
| 1. Malar rash | 1. Acute cutaneous lupus (malar rash or generalized maculopapular rash observed by a clinician) |
| 2. Discoid rash | 2. Subacute cutaneous or discoid lupus |
| 3. Photosensitivity | 3. Fever |
| 4. Oral or nasal ulcerations | 4. Oral ulcers |
| 5. Nonerosive arthritis: Involving two or more joints, characterized by tenderness, swelling or effusion | 5. Synovitis involving two or more joints |
| 6. Pleuritis or pericarditis | 6. Serositis |
| 7. Renal disorders: persistent proteinuria or cellular casts | 7. Renal disorders |
| | 7. Proteinuria >0.5 g/24 h |
| | 8. Acute pericarditis |
| | 9. Pleural or pericardial effusion |
| | 10. Class II or V lupus nephritis on renal biopsy according to ISN/RPS 2003 classification |
| | 11. Class III or IV lupus nephritis on renal biopsy according to International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 |
| | 12. Delirium |
| | 13. Psychosis |
| | 14. Seizure |
| | 15. Leucopenia |
| | 16. Thrombocytopenia |
| | 17. Autoimmune hemolytic anemia |
| | 18. Antinuclear antibodies (ANA) |
| | 19. Low C3 OR low C4 |
| | 20. Low C3 AND low C4 |
| | 21. Anti-dsDNA antibodies antibody positive, by any of the following: - medium or high titer anti-cardiolipin - positive test for anti-beta-2glycoprotein |
| | 22. Positive antiphospholipid antibodies anemia |

(Continued)

increased AST (70 UI/l), ALT (59 UI/l) and bilirubin (total 8.1 mg/dl, direct 5.5 mg/dl), and negative anti-dsDNA and anti-Sm antibodies. The echocardiogram revealed cardiomegaly and pericardial effusion. The presence of fever, palmoplantar erythema with desquamation, perineal erythema, elevated transaminases, gallbladder hydrops and pericardial effusion led to a diagnosis of incomplete KD and intravenous immunoglobulins, aspirin and corticosteroids were administered. On follow up, cardiac and liver abnormalities resolved.

**Case 3**

An 11 year-old-female presented with a history of cervical adenopathy, followed 2 months later by left knee arthritis, malar rash, photosensitivity, dark urine and fever. On physical examination malar rash and intense Raynaud’s phenomenon were noted (Figure 1). The diagnosis of lupus was made based on acute cutaneous lupus - malar erythema and photosensitivity -, arthritis, renal disease - cylindruria and proteinuria -, autoimmune hemolytic anemia, lymphopenia, positive antinuclear antibodies and anti-dsDNA antibodies. During her hospitalization fever continued and she presented erythematosus crusted lips and a generalized rash with palmpoplantar erythema. Intravenous immunoglobulins were administered with a presumptive diagnosis of Parvovirus-B19 infection. Methylprednisolone pulses were started, and improvement was observed. She was discharged with hydroxychloroquine, prednisone and mycophenolate mofetil. She presented periungueal desquamation while at home. One month later, she was readmitted to the hospital due to headache, seizures and persistent hypertension. Echocardiogram and heart MRI revealed large ectasia of the main left coronary artery (z-score +6.12), large ectasia of the circumflex artery (z-score +5.19), with normal proximal right coronary artery and large ectasia of the mid right coronary artery (z-score +7.35) with mild mitral regurgitation (Figure 2).
| References | Gender | Age | KD | SLE | Treatment | Final diagnosis |
|------------|--------|-----|----|-----|-----------|-----------------|
| Laxer et al. (5) | Female | 10 m-5 yo | Fever (7 days), pruritic erythematous maculopapular rash, erythema of the palms and soles, bilateral nongranulatve conjunctivitis, rige posterior cervical lymph node, dry fissured lips, edema of her hands and feet, peeling of the skin over her fingers and toes | 3 years later Fever, anorexia, photosensitivity, facial rash, livedo reticularis, painless palatal ulcer, generalized lymphadenophathy | Aspirin 75 mg for 8 weeks. 3 years later. PDN 2 mg kg day. | KD and SLE |
| Marchetto et al. (7) | Male | 15 yo | Fever, chelitis, strawberry tongue, bilateral non exudative conjunctivitis with hemorrhages in the left eye and diffuse maculopapular rash, hands and feet with periangual digital peeling | Butterfly rash on his face, arthralgia, muscle weakness, headache | IVIG and acetyl salicylic acid. Recurrent KD Methylprednisolone an a second cycle of IVIG | KD |
| Diniz et al. (6) | Female | 13 yo | Fever (7 days), bilateral bulbar nonexudative conjunctivitis, erythema of the oral an pharyngeal mucosa, cervical lymphadenopathy (2cc), erythema of Palms an diffuse maculopapular rash | Irritability, myalgia and arthritis (edema and tenderness in elbows and proximal interphalangeal joints in both hands an ankles), | Hemoglobin 9.7 g/dl Urinalysis: Proteinuria 0.57 g/24 h. Leukocytes 3,000, Erythrocytes 1,000 Positive ANA 1:320, anti-dsDNA 516, anti-Ro. Negative antcardiolipin C3 42, C4 5 | IVIG (2 g/kg do), and aspirin 80 mg/kg day | KD and SLE |
| Diniz et al. (6) | Female | 4 yo | Fever (12 days), bilateral bulbar nonexudative conjunctivitis, chelitis and strawberry tongue, cervical lymphadenopathy (1.5cc), erythema of Palms, diffuse maculopapular rash, desquamation of the fingers and toes and in periangual region. | 1 year later Irritability, Acute swelling of the eyelids, hands and feet, hypertension and pericarditis | Hemoglobin 7.4 g/dl, Leukocytes 3,800, Lymphocytes 874 Urinalysis: Leukocyturia Proteinuria gr/24 h, C3 71 C4, <010 ANA 1:320 Anti-dsDNA 654. | IVIG (2 g/kgdo), and aspirin 80 mg/kg day | KD and SLE |
| Agarwal et al. (8) | Female | 9 yo | Fever (intermittent) Bilateral conjunctival erythema ECHO mild dilatation of the LMCA, and diffuse ectasia of the LAD, mild mitral regurgitation suggestive of carditis. | Abdominal pain arthralgias (ankles, wrists, right knee) weakness of lower extremities aphots ulcer under the tongue | Hemoglobin 11.3 g/dl, Leukocytes 3,100 ANA 1:2560 Positive Coombs Anti- dsDNA >200 | Ethosuximide (discontinued) Intravenous Methylprednisolone pulse therapy (30 mg/kg day) for 3 days. Oral Steroids Methotrexate Hydroxychloroquine Aspirin (81 mg/day) | SLE |
| References            | Gender            | Age | KD                                      | SLE                                      | Treatment                                      | Final diagnosis |
|-----------------------|-------------------|-----|-----------------------------------------|------------------------------------------|------------------------------------------------|-----------------|
| Agarwal et al. (8)    | Female (Family     | 6   | Fever                                   | Arthralgias (Ankle and Knee)            | Hemoglobin 9 g/dL                                | SLE             |
|                       | history for       | y/o | Conjunctivitis non-exudative            | Abdominal PAIN                          | ANA 1:640                                       |                 |
|                       | Lupus and Sarcoidosis) |    | Cervical Adenopathy                     |                                          | Myeloperoxidase antibodies 28 mg/dL             |                 |
|                       |                    |     | Rash                                    |                                          | 4 days later                                    |                 |
|                       |                    |     | 2 days later                             |                                          | 4 days later                                    |                 |
|                       |                    |     | Recurrence of fever                     |                                          | Hemoglobin 9.7 g/dL                             |                 |
|                       |                    |     | 2 days later                             |                                          | platelet count 530 k/ml                        |                 |
|                       |                    |     | Recurrence of Fever                     |                                          | Low C3 complement 64 mg/dL                     |                 |
|                       |                    |     | Sandpaper-like rash                     |                                          | Normal C4 complement                            |                 |
|                       |                    |     | Cervical Lymphadenopathy                 |                                          | ANA 1:2560                                      |                 |
|                       |                    |     | ECHO dilated LMCA                        |                                          | Myeloperoxidases and proteinase 3 antibodies   |                 |
|                       |                    |     |                                          |                                          | negative.                                       |                 |
|                       |                    |     |                                          |                                          | Antibodies-DSdna > 200                          |                 |
|                       |                    |     |                                          |                                          | Positive Combs                                  |                 |
|                       |                    |     |                                          |                                          | Positive ENA-RNP                                 |                 |
|                       |                    |     |                                          |                                          | Intraavenous Gammaglobulin 2 g/kg               |                 |
|                       |                    |     |                                          |                                          | Aspirin                                         |                 |
|                       |                    |     |                                          |                                          | 2 days later                                    |                 |
|                       |                    |     |                                          |                                          | Intravenous Gammaglobulin 2 g/kg                |                 |
|                       |                    |     |                                          |                                          | Aspirin                                         |                 |
|                       |                    |     |                                          |                                          | 2 days later                                    |                 |
|                       |                    |     |                                          |                                          | Intravenous Methylprednisolone pulse therapy   |                 |
|                       |                    |     |                                          |                                          | (30 mg/kg/day) for 3 days.                      |                 |
|                       |                    |     |                                          |                                          | Oral Steroids                                   |                 |
|                       |                    |     |                                          |                                          | Hydroxychloroquine                              |                 |
|                       |                    |     |                                          |                                          | Aspirin 81 mg (daily)                           |                 |
|                       |                    |     |                                          |                                          | Methotrexate                                    |                 |
| Agarwal et al. (8)    | Male (Family history for Lupus and Sarcoidosis) | 13 | Eczema                                  | Joint pains                                  | Hemoglobin 4.9 g/dL                             | SLE             |
|                       |                    | y/o | Fever (intermittent)                     | Swelling of his hands and feet            | ANA 1:1280                                      |                 |
|                       |                    |     | Pruritic Rash                            |                                          | Positive Coombs                                 |                 |
|                       |                    |     | Chill                                    |                                          | Antibodies-dsDNA > 200                         |                 |
|                       |                    |     | Bilaterally injected sclera              |                                          | Positive antcardioplin IgM, anti-Sm, anti-RNP, |                 |
|                       |                    |     | Cervical Lymphadenopathy                 |                                          | anti-SSA and β2-glycoprotein-1 antibodies.     |                 |
|                       |                    |     | Bullous pemphigoid rash to the extremities |                                          | C3 20 mg/dL                                     | SLE             |
|                       |                    |     | Non pitting edema of lower extremities   |                                          | C4 < 2 mg/dL                                    |                 |
|                       |                    |     | ECHO showed dilatation of the LMCA, LAD, |                                          | Intravenous methylprednisolone pulse therapy   |                 |
|                       |                    |     | and RCA without pericardial effusion,    |                                          | (30 mg/kg/day) for 3 days.                      |                 |
|                       |                    |     | mild tricuspid insufficiency.            |                                          | Rituximab (750 mg/m²) on day 3 of steroid pulse, |                 |
|                       |                    |     |                                          |                                          | and a second dose given 2 weeks after Oral    |                 |
|                       |                    |     |                                          |                                          | PDN                                             |                 |
|                       |                    |     |                                          |                                          | Oral Enalapril                                   |                 |
|                       |                    |     |                                          |                                          | Hydroxychloroquine                              |                 |
|                       |                    |     |                                          |                                          | Aspirin 81 mg/day                                |                 |
|                       |                    |     |                                          |                                          | 2 months later                                  |                 |
|                       |                    |     |                                          |                                          | Mofetil mycophenolate                            |                 |
| Agarwal et al. (8)    | Female (Family history was notable for mother deceased due to complications of Rheumatoid Arthritis, SLE, Sjögren’s syndrome, and dialysis-dependent end-stage renal disease). | 13 | Fever                                   | Headaches, swelling of both legs, bilateral synovitis of the elbows | Hemoglobin 6 g/dL | SLE             |
|                       |                    | y/o | Raynaud’s phenomenon                    |                                          | BUN 33 mg/dL                                    |                 |
|                       |                    |     | Bilateral pruritic rash on her lower extremities |                                          | Cr 1.87 mg/dL                                   |                 |
|                       |                    |     | Periorbital Edema                       |                                          | Urinalysis hematuria an proteinuria > 300 mg/dL|                 |
|                       |                    |     | ECHO demonstrated dilatation of the LMCA, LAD, and RCA, with perivascular echogenic brightness around the coronary branches, Borderline Leith ventricular hypertrophy and small circumferential pericardial effusion. | | ANA 1:2560                                      |                 |
|                       |                    |     |                                          |                                          | Positive Coombs                                 |                 |
|                       |                    |     |                                          |                                          | Antibodies-dsDNA > 200                          |                 |
|                       |                    |     |                                          |                                          | Positive RNP                                     |                 |
|                       |                    |     |                                          |                                          | Positive anti-Sm anti-Ro antibodies.            |                 |
|                       |                    |     |                                          |                                          | C3 17 mg/dL                                     |                 |
|                       |                    |     |                                          |                                          | C4 2 mg/dL                                      |                 |
|                       |                    |     |                                          |                                          | Intravenous Methylprednisolone pulse therapy    |                 |
|                       |                    |     |                                          |                                          | (2 mg/kg/day) for 3 days.                       |                 |
|                       |                    |     |                                          |                                          | Oral enalapril                                   |                 |
|                       |                    |     |                                          |                                          | Oral PDN                                        |                 |
|                       |                    |     |                                          |                                          | Furosemide                                      |                 |
|                       |                    |     |                                          |                                          | Hydroxychloroquine                              |                 |
|                       |                    |     |                                          |                                          | Mofetil mycophenolate                            |                 | (Continued)
| References       | Gender | Age  | KD                          | SLE                                  | Treatment                                                                 | Final diagnosis |
|------------------|--------|------|-----------------------------|--------------------------------------|---------------------------------------------------------------------------|-----------------|
| Zhang et al. (9) | Male   | 13 yo| Fever, rash, non-exudative  | Erythema, hepatosplenicomegaly       | Intravenous methylprednisolone.                                           | SLE (and KD?)   |
|                  |        |      | conjunctivitis, cervical    |                                      |                                                                           |                 |
|                  |        |      | lymph adenopathy. arthralgia.|                                      |                                                                           |                 |
|                  |        |      |                              |                                      |                                                                           |                 |
| Case 1           | Male   | 16 yo| Fever (1 month), painful    | Malar erythema, Seizures and        | IVIG (2 g/kg/dose), and aspirin 80 mg/kg/day later                        | SLE             |
|                  |        |      | cervical lymph nodes, rash  | deterioration of neurological, Aseptic|                                                                           |                 |
|                  |        |      | on the trunk and extremities,| meningitis                           |                                                                           |                 |
|                  |        |      | conjunctival injection,     |                                      |                                                                           |                 |
|                  |        |      | cracked lips, oral mucosa   |                                      |                                                                           |                 |
|                  |        |      | erythematous                |                                      |                                                                           |                 |
| Case 2           | Male   | 12 yo| Fever                       | Pleural and pericardial effusions,  | Pancytopenia, Positive ANA                                               | KD              |
|                  |        |      | Palmoplantar erythema,      | oral ulcers                          |                                                                           |                 |
|                  |        |      | desquamation hands and feet |                                      |                                                                           |                 |
|                  |        |      | Perineal erythema,          |                                      |                                                                           |                 |
|                  |        |      | Gallbladder hydrops         |                                      |                                                                           |                 |
| Case 3           | Female | 11 yo| Fever, generalized rash,    | Malar rash, Raynaud’s phenomenon,    | Methylprednisolone pulses IVIG                                            | SLE and KD      |
|                  |        |      | cervical lymphadenopathy,   | livedo reticularis                  |                                                                           |                 |
|                  |        |      | palmoplantar erythema,      |                                      |                                                                           |                 |
|                  |        |      | erythematous lips,          |                                      |                                                                           |                 |
|                  |        |      | desquamation hands          |                                      |                                                                           |                 |

IVIG, intravenous immunoglobulins; PDN, Prednisone; ANA, antinuclear antibodies.

ECHO, LMCA, Left main coronary artery; LAD, proximal left Anterior descending coronary artery; RCA, proximal right coronary arteria.
DISCUSSION

Clinical criteria are used to diagnose KD with the presence of fever and principal clinical features involving the mouth, eyes, skin, hands and feet and cervical lymphadenopathy (Table 1). SLE is a complex autoimmune disease with variable clinical features. In the absence of SLE diagnostic criteria, SLE classification criteria are often used by clinicians to help identify some of the salient clinical features when making the diagnosis. Children who fulfill the ACR criteria, SLICC criteria or the new EULAR/ACR criteria are considered to have definitive SLE (Table 2). Of note is that in the recent EULAR/ACR criteria, fever is considered a criterion suggestive of SLE.

KD and SLE share several clinical manifestations: both diseases can present with fever, lymphadenopathy, arthritis or arthralgia, ocular and mucosal manifestations, rash and multisystemin involvement. However, the coexistence of both or misdiagnosis among them has seldom been reported (5–9). There are two previously reported cases of lupus-onset mimicking Kawasaki disease and vice versa and another three reported cases of the coexistence of both diseases (5–9) (Table 3).

The first patient was diagnosed with SLE and KD in an almost concurrent presentation, since she presented diagnostic criteria for both diseases. It can be discussed whether this case could only correspond to lupus with carditis, as the ones reported by Agarwal et al., however it is important to note that none of the four patients described by this author completed diagnostic criteria for KD (8). Recently, Zhang et al. (9) report a 13-year-old male who presented fever, rash, non-exudative conjunctivitis with cervical lymphadenopathy and an echocardiogram presenting coronary artery dilation. He was eventually diagnosed as SLE since he presented autoimmune hemolytic anemia, positive ANA, dsDNA and hypocomplementemintia (9). As can be seen from previous reports (Table 3), both diseases can present simultaneously or with years of difference (5, 6, 9).

Coronary arteritis is not an exclusive feature of KD as other diseases like lupus and other vasculitis present this complication. In fact, coronary artery lesions have been documented in asymptomatic patients with microscopic polyangiitis, polyarteritis nodosa, and Wegener granulomatosis with MRI (10). Children with systemic onset juvenile idiopathic arthritis may present coronary artery dilation on echocardiograms similar to that observed for children with KD (11).

In our second patient the initial clinical picture made KD a diagnostic possibility; the skin biopsy was useful, as features were unequivocal for lupus. Parotitis was an unusual manifestation and can be present in both KD and lupus (12, 13). The third case was initially diagnosed as SLE, but eventually the clinical picture - despite atypical features such as pleural effusion, the response to treatment and the current health status under no medication, are more compatible with atypical KD (14).

Both KD and SLE share common features in terms of mechanisms of vascular inflammation and both may present with coronary artery dilatation. The two of them have been associated with the presence of anti-peroxiredoxin antibodies and the elevation of IL-17 (15, 16).

At this point, with the previously reported cases and our own it can be said that both diseases may mimic each other’s clinical presentation. Interestingly, the majority of the patients that often present with the clinical challenge were tweens and teenagers (an unusual age for KD). KD in adolescence presents with atypical signs, incomplete presentation, and develop coronary complications more commonly (17). An adolescent with fever and rash should include KD and SLE in the differential diagnosis. As always in medicine, an accurate diagnosis is necessary to give appropriate treatment and reduce complications.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

Signed informed consent was obtained from the parents and the patients.

AUTHOR CONTRIBUTIONS

MY-N, MS, and MP-H conceptualized and designed the study, reviewed, and revised the manuscript. MS and MY-N carried out the initial analyses and drafted the initial manuscript. FR-L and MG-G critically reviewed the manuscript. MP-H, EV-M, and MG-D recollected the data. All the authors were responsible for the treatment of the patient and read and approved the final manuscript.

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**Conflict of Interest:** MY-N has received lecture fees from Shire, CSL Behring and Octapharma.

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