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CASE REPORT

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Pediatric Onset Systemic Lupus Erythematosus Complicated by Toxic Epidermal Necrolysis: A Rare Association*

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ABSTRACT

Toxic epidermal necrolysis (TEN) and systemic lupus erythematosus (SLE) rarely coexist in pediatric patients, posing significant diagnostic dilemma due to their overlapping clinical manifestations, particularly in the bullous subtype. We report a case of a 14-year-old female initially presenting with features suggestive of Bullous SLE, including generalized erythematous plaques and subsequent bullae formation, accompanied by systemic symptoms and positive serological markers for SLE. However, skin biopsy findings revealed characteristics consistent with TEN, precipitated by recent antibiotic administration for a urinary tract infection. Prompt cessation of offending medications and initiation of appropriate therapy led to clinical improvement. TEN in pediatric population with SLE is uncommon but possible occurrence. Thorough history including drug history, physical examination and proper work-up help differentiate these two or discover their coexistence.

Keywords: toxic epidermal necrolysis, systemic lupus erythematosus, pediatric SLE, toxic epidermal necrolysis in systemic lupus erythematosus

INTRODUCTION

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening dermatological conditions, characterized by extensive necrosis, epidermal detachment and mucosal erosions. The underlying etiology is most often secondary to various drugs.[1] However, *Mycoplasma pneumoniae* infection, vaccinations, acute graft-vs-host disease, and autoimmune diseases such as systemic lupus erythematosus (SLE) have been reported as rarer causes. In previous studies, SLE appears to confer a higher risk of development of drug-induced TEN and has been attributed as a co-factor.[2]

SLE is a chronic autoimmune disease of unknown etiology that affects almost all organs. It is characterized by abnormal autoimmune antibodies and varied clinical manifestations.[1] While SJS/ TEN is rare, the co-existence of SJS/TEN in context of childhood-onset lupus is distinctly unusual and only a handful of cases have been reported in the literature. As the presentation of both illnesses can be heterogenous, simultaneous occurrence of both diseases in the same patient can pose diagnostic difficulties.[3]

In this paper, we present the diagnostic approach, histopathologic findings, and treatment in a case of a 14-year-old female with SLE complicated by TEN.

CASE

A 14-year-old Filipino, female, admitted by the Pediatric service as a new case of Systemic Lupus Erythematosus. She was diagnosed based on the American College of Rheumatology's (ACR) classification criteria for SLE (malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, renal, hematologic and immunologic disorders) with a score of 9 out of 11. Autoimmune markers were positive for anti-nuclear antibody (ANA) and anti-double stranded DNA (anti-dsDNA). Serum Complement C3 was decreased (Appendix). She was referred to dermatology service due to multiple erythematous annular plaques and patches, some with dusky centers and crusts on face, trunk, both upper and lower extremities (Figure 1). Also noted were painless palatal erosion, facial and periorbital edema, and periungual erythema on all fingers of both hands. The patient previously presented with a five-week history of on-and-off undocumented fever, bilateral knee joint pains graded 10/10, chills and weakness with multiple erythematous patches and plaques on face, trunk and upper and lower extremities.

Upon admission, the patient was started on Ceftazidime 2g IV every 12 hours and Gentamicin 60 mg IV every 8 hours for urinary tract infection. Clobetasol propionate 0.05% ointment mixed with plain petroleum jelly and Mometasone furoate 1% cream mixed in moisturizing lotion were applied twice daily on the body and face, respectively. Application of broad-spectrum sunscreen SPF 50 every 2-4 hours and oral hygiene with Chlorhexidine mouthwash were advised. Four days later, she developed vesicles and bullae on the previous erythematous patches and plaques located on the back. This was associated with undocumented fever. An initial diagnosis of Bullous Systemic Lupus Erythematosus was made. On day 6 of antibiotics, flaccid vesicles and bullae developed on the trunk and both upper and lower extremities. Lesions on the posterior trunk progressed to epidermal detachment (Figure 2). Nikolsky and Asboe Hansen signs were positive. Palatal erosion also increased in size and became painful. At this point, a diagnosis of Toxic Epidermal Necrolysis in SLE with >30% total body surface area (TBSA) involvement was made. It was confirmed by 4-mm skin punch biopsy revealing orthokeratosis and focal parakeratosis on top of tiers of epidermal necrosis. Vacuolar interface was seen in the dermo-epidermal junction with necrotic keratinocytes and perivascular lymphocytic infiltrates (Figure 3). In contrast to bullous SLE, which typically shows subepidermal blister with predominantly neutrophilic infiltrate and vacuolar degeneration. Direct immunofluorescence was requested to further investigate the presence of lupus erythematosus. However, due to financial limitations of the family, this was not done. Prednisone 40 mg/tab daily (1.0 mg/kg/day) was started. Additionally, medications (intravenous antibiotics) that might have triggered the condition were discontinued and shifted to Oxacillin 2 g IV every 6 hours to treat the urinary tract infection for 7 days. Repeat urinalysis after 7 days showed resolution of the infection. Given the co-existence of SLE, Mycophenolate mofetil 500 mg/tab twice daily and Hydroxychloroquine 100 mg/tab, 2 tablets once daily were initiated.

Other work-ups showed leukopenia, anemia, elevated liver enzymes and fasting blood sugar, proteinuria and presence of urinary casts. Creatinine, blood urea, serum electrolytes, blood culture, peripheral blood smear and chest radiograph were normal.

On day 7 of treatment, there was gradual clinical improvement as evidenced by post-inflammatory hyperpigmented and hypopigmented patches (Figure 4) and biochemical improvement. She was discharged with tapering doses of Prednisone with no recurrence of cutaneous lesions.

DISCUSSION

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare life threatening dermatologic conditions with incidence ranging from 1.2 to 6 and 0.4 to 1.2 per million person-years, respectively. Incidence in the Philippines, Malaysia and Taiwan is approximately ten

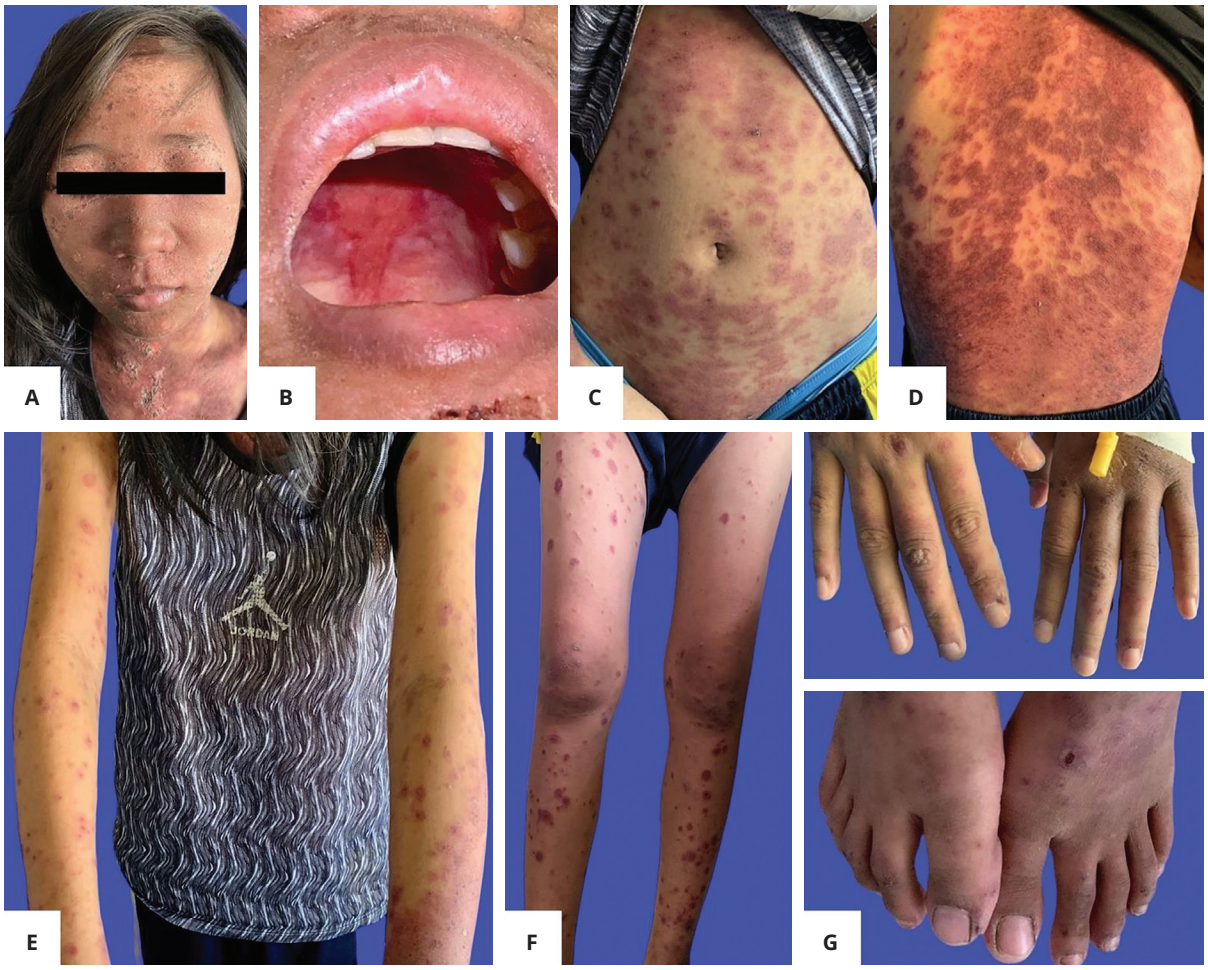

Figure 1. Referral Day 1 – **(A)** Multiple erythematous to violaceous patches and plaques with dusky centers and crusting on the face with periorbital and facial edema; **(B)** palatal erosion; **(C)** similar lesions on the anterior trunk; **(D)** confluent patches and plaques on the posterior trunk; **(E)** lesions on the upper extremities; **(F)** lesions on the lower extremities; and **(G)** periungual erythema with edema of all fingers and toes.

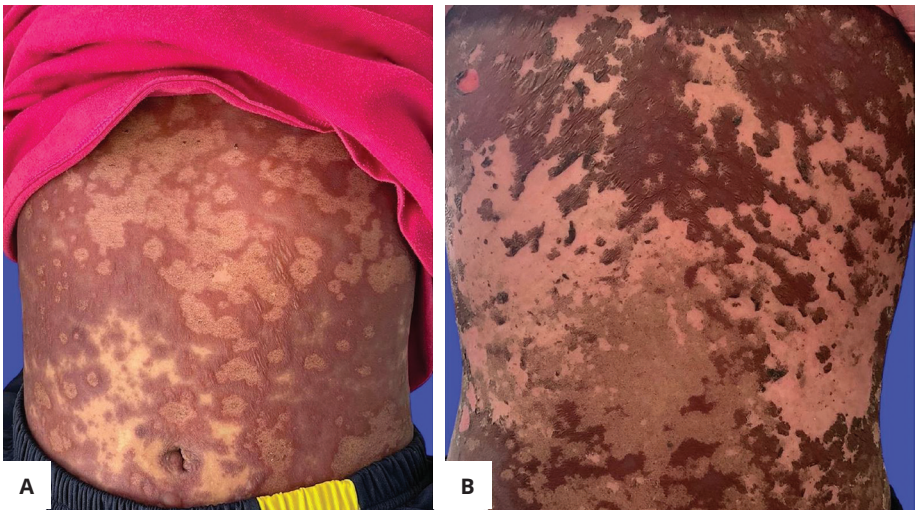

Figure 2. **(A)** Flaccid bullae on anterior trunk. **(B)** Epidermal detachment on posterior trunk.

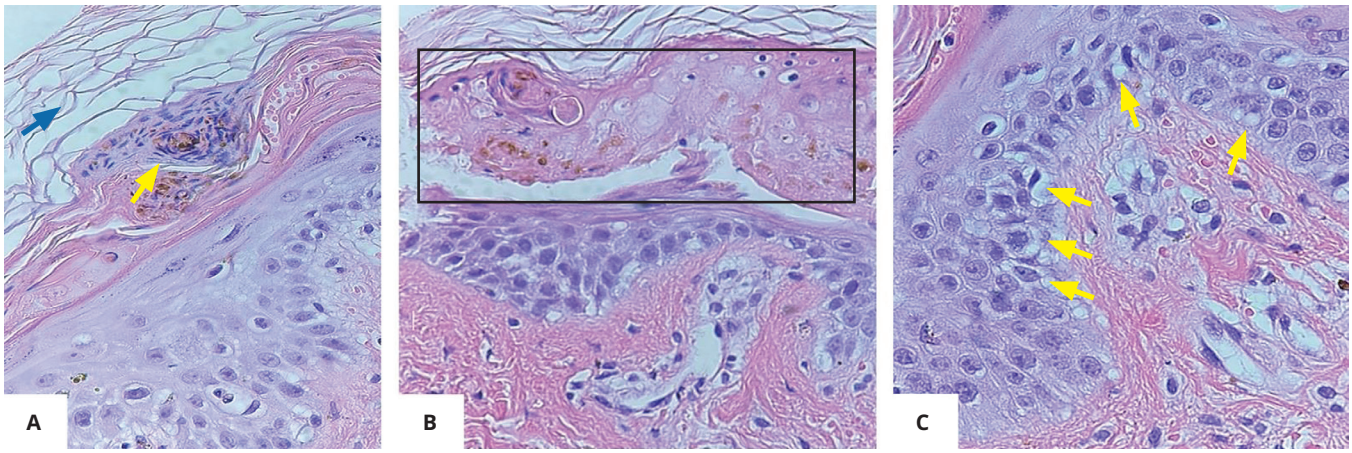

Figure 3. H&E 100x. **(A)** Orthokeratosis *(blue arrow)* and focal parakeratosis *(yellow arrow)* in the epidermis. **(B)** Areas of epidermal necrosis with loss of keratonicytes *(highlighted in the inset)*. **(C)** Vacuolar interface in dermo-epidermal junction, indicating interface dermatitis *(yellow arrows)*.

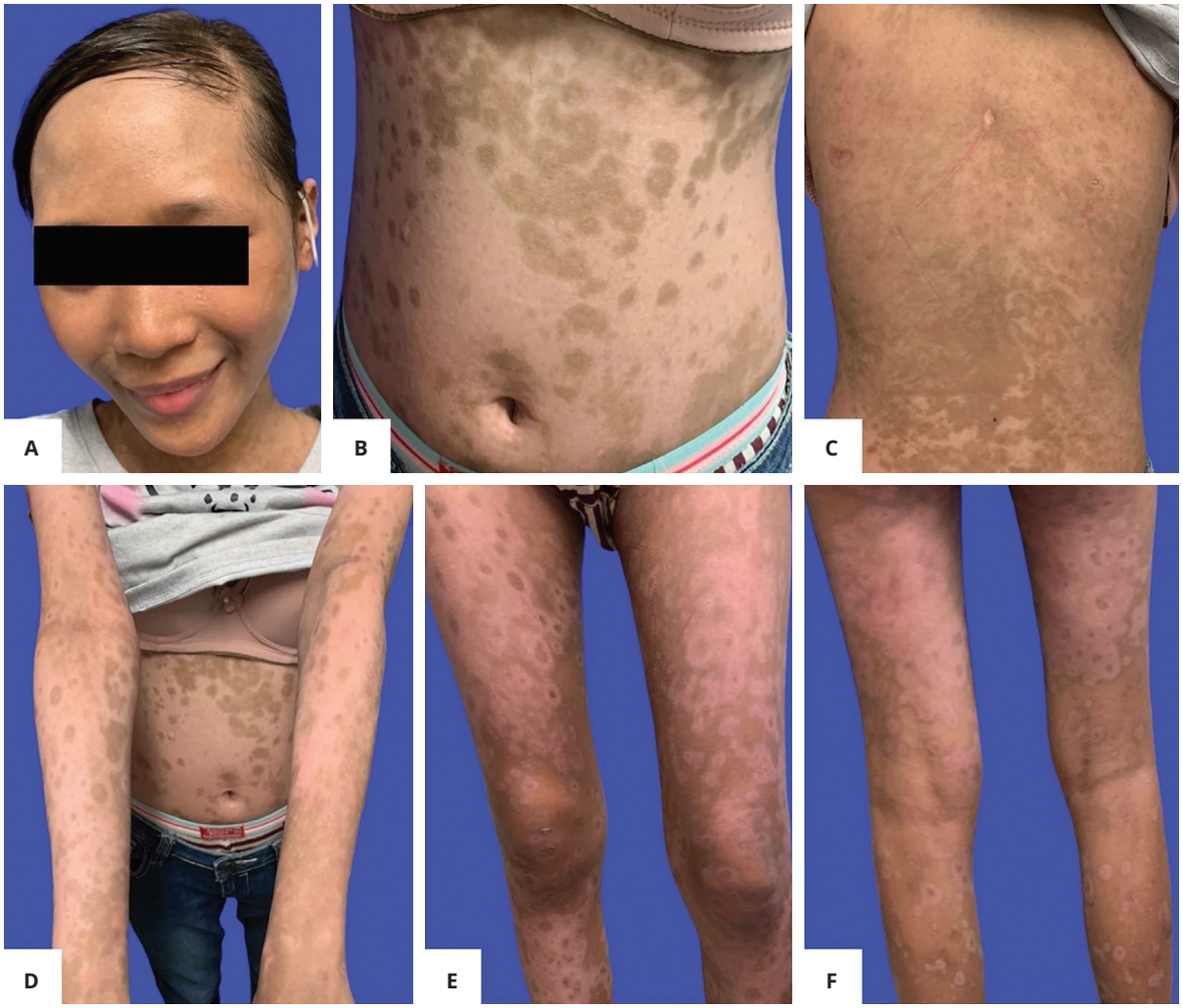

Figure 4. Three weeks after topical corticosteroids and systemic immunomodulators. **(A)** hyperpigmented and hypopigmented patches on the face; **(B)** anterior trunk; **(C)** posterior trunk; **(D)** upper extremities; and **(E, F)** lower extremities.

times higher than those reported in Caucasian countries. The mortality rate has been documented at 4.7% for SJS and 16.7% for TEN.[4]

Patients typically display an acute onset, with skin lesions characterized by erythematous or violaceous patches, atypical targetoid lesions, bullae, erosions and skin detachment.[5] The affected body surface area differentiates pure SJS (<10%) from pure TEN (>30%). Complications and death typically arise from infections related to loss of the skin barrier.[6]

The scarcity of literature and researches involving the pediatric population is likely related to the lower incidence of SJS/TEN in children. Furthermore, in our case, simultaneous occurrence of TEN and SLE in a pediatric patient is considerably more uncommon. SLE is associated with an increased risk of SJS/TEN and predisposes patients to a higher likelihood of developing drug-induced TEN.[2] A disrupted regulatory immune function amplifies cytotoxic responses, thereby promoting the onset of SJS/TEN and contributing to the overall heightened susceptibility observed in patients with autoimmune diseases.[7] In the study by Tanaka, SLE had an odds ratio of 5.34 for SJS and an odds ratio close to one for TEN.[8] The etiology of SJS/TEN varies, including infections, drugs, and vaccines, with medications considered the most common cause.[9]

TEN and SLE are inflammatory dermatoses characterized by keratinocyte apoptosis. In TEN, the complex mechanism involves apoptosis initiated by cytotoxic T cells through mediators like granulysin and granzyme, along with Fas-Fas ligand interactions. Similar mediators are found in SLE. This overlap in cytotoxic and cytokine-mediated mechanisms highlights a common immunologic pathway underlying epidermal injury in both conditions. In cutaneous lupus, UV damage triggers apoptosis, necrosis, and an increase in chemokines such as CCL27. This activates autoimmune T cells and interferon-alpha-producing dendritic cells leading to an amplification of cytokine release. Fas expression is notably high in acute cutaneous lupus.[8]

TEN can be diagnosed clinically while histopathology and molecular testing may be performed to confirm the diagnosis. It is important to differentiate this case to LE-specific vesiculobullous diseases such as Bullous SLE (BSLE), TEN-like SLE, acute cutaneous lupus erythematous (ACLE), and other autoimmune vesiculobullous diseases. Bullous eruptions in the setting of SLE during its early presentation, posed a significant diagnostic challenge as highlighted by this case. LE-specific vesiculobullous lesions usually begin on photodistributed areas and then spread symmetrically. Mucosal involvement is typically absent or minimal. Our initial working impression was BSLE due to the acute onset of widespread vesiculobullous lesions on sun-exposed areas in the setting of SLE.[10] However, given the rapid cutaneous progression, prominent mucosal involvement, and recent high-risk drug exposure, we favored SJS/TEN as opposed to BSLE. This diagnosis was supported by positive Nikolsky and Asboe Hansen signs and characteristic histopathological findings.

The primary goal in the treatment of SJS/TEN is to identify and discontinue, if there is any, the offending medication(s) and ensure appropriate symptomatic supportive therapy, pain management, and prevention of infection. Adjuvant therapies include systemic corticosteroids, immunosuppressants, tumor necrosis factor inhibitors, and plasmapheresis, as well as intravenous immunoglobulin (IVIG), which can inhibit the apoptosis of keratinocytes.[1] A recent systematic review and meta-analysis glucocorticosteroids and cyclosporine were the most promising systemic immunomodulating therapies for SJS/ TEN, while no significant benefits were observed for other therapies, including IVIG.[1] In our patient, oral glucocorticoids were given to treat TEN, which are also in the management of SLE. Additional immunosuppressants such as Mycophenolate mofetil and Hydroxychloroquine, were given to treat the patient's SLE.

The patient responded well to treatment with supportive care, topical and oral corticosteroids, and immunosuppressive drugs. The lesions had mostly resolved with minimal residual scarring, postinflammatory hyperpigmentation and hypopigmentation after 3 weeks. Mild lesions in SJS/TEN usually heal within weeks, with no functional loss if ocular involvement is absent, but minimal scarring may occur. However, life-threatening sequelae such as sepsis and systemic organ failure may occur in severe cases.

CONCLUSION

Stevens–Johnson syndrome and toxic epidermal necrolysis are rare dermatologic emergencies. SJS/TEN in a pediatric population with a simultaneous occurrence of Systemic Lupus Erythematous is an even rarer condition, thus high level of suspicion should be entertained if both diseases are present. To prevent complications, early diagnosis, identification and discontinuation of triggers and prompt treatment are required. Dermatologists play a vital role in the prompt diagnosis and management of these life-threatening cutaneous conditions. However, an interprofessional team approach is still necessary for the best outcomes. This study adds to the limited literature available on the co-existence of these two challenging dermatologic diseases in pediatric patients.

RECOMMENDATION

In rare cases of Toxic Epidermal Necrolysis (TEN) and a concurrent Systemic Lupus Erythematosus (SLE), it is essential to perform a Direct Immunofluorescence (DIF) to further confirm their coexistence. Furthermore, after initiating treatment, it is strongly recommended to repeat serological assessments, including Antinuclear Antibodies (ANA), anti-dsDNA, and complement C3 levels. This re-evaluation will help determine any changes in the patient's autoimmune status post-treatment, guiding further management decisions and assessing disease activity. Monitoring these parameters is vital, as it allows the physician and/or dermatologist to identify potential lupus flares early and adjust therapeutic strategies accordingly, thereby optimizing patient care and outcomes.

Ethical Consideration
Informed consent was obtained from the patient and patient's mother before submission of manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
The authors declared no conflict of interest.

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APPENDIX

Laboratory results

Table A. Complete blood count

	Normal range	Results			
		1st	2nd	3rd	4th
WBC	4-10 x 10^9/L	4.0	3.6	3.9	8.3
RBC	4-5.4 x 10^{12}/L	4.0	3	3.1	3.4
Hemoglobin	120-160 g/L	111	85	89	99
Hematocrit	0.37-0.47	0.36	0.27	0.28	0.31
Platelet	108-282 x 10^9/L	240	190	204	370

Table B. Blood chemistry

	Normal range	Results
Na	135-148 mmol/L	142.30
K	3.50-5.30 mmol/L	3.76
Cl	98-107 mmol/L	106.10
iCa	1.13-1.32 mmol/L	1.10
Creatinine	53.05-106.10 umol/L	84.78
Urea	1.67-8.35 mmol/L	4.66
SGPT (ALT)	0-49 U/L	90
SGOT (AST)	0-46 U/L	379
FBS	3.89-5.83 mmol/L	6.16

Table C. Serology

	Normal range	Results
ANA	<80	640 (Homogenous)
Anti-dsDNA	<30 IU/ml	301.25 (strong positive)
Serum C3	83-193 mg/dL	

Table D. Urinalysis

	Initial	Repeat after antibiotics
Color	Dark Yellow	Yellow
Transparency	Turbid	Slightly Turbid
Blood	+	+
Bilirubin	Negative	Negative
Urobilinogen	4.0	Normal
Ketones	+	Negative
Protein	++	+
Nitrite	Negative	Negative
Glucose	Negative	Negative
pH	6.0	7.5
Specific gravity	1.030	1.020
Leukocyte	++	Trace
RBC	26	25
Pus	203	30
Epithelial cells	10	50
Bacteria	535	10
Hyaline cast	0	0
Coarse granular cast	15-20	0
Fine granular cast	0-1	0
Waxy Cast	0-1	0

Table E. Chest X-ray

Chest X-ray (PA, LAT)	No definite chest radiographic abnormality detected.