From Telemedicine to the ICU—Fever and Rash in a 9-Year-Old Girl

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A 9-year-old girl presented to her primary care pediatrician via telemedicine during the initial months of the coronavirus disease 2019 pandemic because of 4 days of warmth perceived by her mother, decreased energy, and a new rash on her upper extremities. After 10 additional days of documented fever >38°C, worsening fatigue, and 1 day of nausea, vomiting, and diarrhea, she was allowed to schedule an in-person visit with her pediatrician after testing negative for severe acute respiratory syndrome coronavirus 2. She appeared ill on arrival to clinic, and her pediatrician recommended evaluation in an emergency department. Her initial laboratory testing revealed nonspecific elevation in several inflammatory markers and leukopenia, and she responded well to intravenous hydration. Over the next 2 weeks, her fever persisted, constitutional symptoms worsened, and she developed progressively painful cervical lymphadenopathy and pancytopenia. She was evaluated in clinic by several specialists and eventually was urged to present to the emergency department again, at which time she was admitted to the PICU. After consulting additional specialists and waiting for laboratory results, the team reached a definitive diagnosis and initiated therapy; however, she experienced rapid clinical decline shortly thereafter. The specialists who assisted with identification of the underlying etiology of her symptoms were able to work together to manage the subsequent complications.

CASE HISTORY WITH SUBSPECIALTY INPUT

Dr Salvador Maffei, Pediatric Resident, Moderator

A previously healthy 9-year-old girl presented to her primary care pediatrician (PCP) with 10 days of fever and red, blanching, and macular rash, along with 1 day of nausea, vomiting, and diarrhea. She had been in her usual state of health until 2 weeks previous, when she seemed less energetic and warm to the touch. Four days into the illness, she visited her PCP via telemedicine and was diagnosed with a viral upper respiratory tract infection. Since the appointment, her measured temperature was >38.0°C daily (maximum 39.5°C), and the rash spread from her upper extremities to her trunk and face. To schedule an in-person visit, she tested negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). After examination in clinic, her PCP urged the family to seek care in the emergency department (ED).

On arrival to the ED, vital signs were pulse 121 beats per minute, temperature 37.5°C, respiratory rate 24 breaths per minute, and blood pressure 88/57 mm Hg. Physical examination revealed cracked lips, red ulcers on her hard palate, anterior cervical lymphadenopathy, and hyperpigmented, blanching macules on her cheeks and arms. Laboratory evaluation (Table 1)

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TABLE 1 A Selection of Laboratory Values Obtained in the ED to Evaluate Systemic Inflammation and Persistent Fever

Laboratory Test	Value	Reference Range
Hemoglobin, g/dL	10.6	10.6–13.4
WBC, cells/μL	3.91	4.27–11.4 × 10^3
Platelets, cells/μL	239	199–369 × 10^3
Ferritin, ng/mL	179	10–60
LDH, U/L	1088	140–280
D-Dimer, μg/mL	1.14	<0.40
AST, U/L	25	11–28
ALT, U/L	61	15–40
SUN, mg/dL	10	2–23
Creatinine, mg/dL	0.42	0.30–0.60
CRP, mg/dL	<0.5	<1.0
Procalcitonin, ng/mL	0.11	0.05–2.00
Troponin, ng/mL	<0.010	<0.030

CRP, C-reactive protein.

demonstrated leukopenia and elevations in ferritin, lactate dehydrogenase (LDH), D-dimer, and alanine aminotransferase (ALT). She had a normal chest radiograph, point of care cardiac ultrasound revealed normal qualitative left ventricular function without evidence of coronary artery dilation, and urinalysis result was positive only for ketones. Repeat polymerase chain reaction (PCR) testing and both immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies to SARS-CoV-2 were negative. Tachycardia, tachypnea, and general appearance improved after receiving an intravenous bolus of normal saline.

Dr De Guzman, what symptoms and laboratory findings should raise concern for multisystem inflammatory syndrome in children (MIS-C)?

Dr Marietta De Guzman, Pediatric Rheumatology

As a recently identified disease process related to infection with SARS-CoV-2, clinicians have relied on a consensus statement from the American College of Rheumatology for diagnostic guidance and initial management strategy.[1] MIS-C should be suspected in pediatric patients with fever (temperature >38.0°C), an epidemiological link to SARS-CoV-2, and inflammation of multiple organ systems, which can be identified on physical examination and laboratory analysis with cardiac biomarkers, liver panel, and acute phase reactants.

In her case, persistent fever, rash, oral mucosal inflammation, and gastrointestinal symptoms warranted evaluation for MIS-C. Although slight elevations in several inflammatory markers were identified, she had negative IgM and IgG antibodies to SARS-CoV-2, 2 negative PCR test results for SARS-CoV-2, and no known contact with a person infected with SARS-CoV-2. The insidious onset of symptoms, persistent negative testing for SARS-CoV-2, and improvement of symptoms with intravenous hydration all would be more consistent with an alternative diagnosis to MIS-C.

Dr Maffei

Following her clinical improvement, she was tested for antibodies to *Rickettsia typhi* and was discharged with a prescription for doxycycline. Unfortunately, her fever returned after 2 days, and she was referred to infectious disease (ID) clinic for additional evaluation.

Dr Rochat, how does an infection with R typhi typically present? What initial testing and treatment should occur?

Dr Ryan Rochat, Pediatric Infectious Disease

R typhi, a flea-borne bacterial species endemic to tropical, coastal regions of the world, causes murine typhus, an illness that typically presents with fever, fatigue, red rash, anorexia, nausea, and vomiting. Aside from living in Texas, an endemic area with rapidly increasing numbers of identified cases, she did not have any pets, known exposure to rodents, or significant time spent outdoors. Given the constellation of symptoms and the importance of early treatment to minimize morbidity and mortality, initiation of doxycycline (the treatment of murine typhus) would be an appropriate first step while awaiting results.[2] Of note, antibody testing for *R typhi* may be negative in the acute phase of illness, and a rise in titers may only be seen 14 days after infection. For this patient with negative IgM and IgG antibodies 2 weeks after symptom onset and recrudescence of fever despite several days of doxycycline, murine typhus was effectively ruled out.

For which additional infections should she be evaluated at this point?

The most likely viral causes of fever and lymphadenopathy for patients who present in the summer include Ebstein-Barr virus, cytomegalovirus (CMV), enterovirus, adenovirus, and parvovirus.[3] In addition, she had a notable exposure of her grandfather, who had emigrated from Southeast Asia and had tested positive for tuberculosis within the past 5 years. Testing with interferon-γ release assay, the gold standard for diagnosis of tuberculosis, was indicated.

Dr Maffei

After her ID clinic appointment, she began to fall behind with her online education, was struggling to sleep, and required liquid meal replacement for nutrition. Repeat complete blood cell count obtained in ID clinic revealed decreased hemoglobin to 9.6 g/dL and worsening leukopenia with lymphocytopenia. IgM and IgG antibodies to CMV were positive, but quantitative CMV PCR was undetectable. The remainder of testing for infectious organisms was negative. Because of anemia, leukopenia, cervical lymphadenopathy, and persistent

anorexia, she was referred urgently to hematology and oncology clinic.

Dr Tran, what would be the next steps to evaluate anemia, leukopenia, and lymphadenopathy?

Dr Jennifer Tran, Pediatric Hematology and Oncology

Obtaining a reticulocyte panel could determine if her dropping counts were related to decreased production or increased destruction of red blood cells. A low or normal reticulocyte count could point toward a neoplastic infiltration of bone marrow, and her insidious onset of constitutional symptoms, lymphadenopathy, and rash would be concerning for acute leukemia. However, she had multiple peripheral smears that did not demonstrate blasts or other neoplastic cells. Transient bone marrow failure also can occur during the active or convalescent phase of many viral infections, and erythropoiesis could be suppressed in many systemic inflammatory conditions.

Her persistently low white blood cell count (WBC), predominant lymphocytopenia, and anterior cervical lymphadenopathy also raised concerns for lymphoma. She was scheduled for computed tomography (CT) of her neck, chest, abdomen, and pelvis. Ultimately, performing an excisional biopsy of a prominent lymph node and examining the histology could help elucidate whether an oncologic, autoimmune, or infectious process was the most likely etiology.

Dr Maffei

On arrival to clinic, she was ill-appearing and dehydrated, requiring fluid resuscitation and stabilization in the ED before imaging could be obtained. She received 3 boluses of normal saline over 6 hours but remained tachycardic and tachypneic. Complete blood cell count was notable for pancytopenia, and aspartate aminotransferase (AST), ALT, ferritin, and D-dimer were noted to have increased (Table 2).

She developed epistaxis after repeat testing for SARS-CoV-2, and repeat hemoglobin was 6.1 g/dL with a low absolute reticulocyte count of 0.026×10^6 cells/μL (reference range: 0.042–0.070) and low reticulocyte percentage of 0.89% (reference range: 0.98%–1.94%). In preparation for transfusion of red blood cells, blood type and antibody screen were ordered and resulted a positive direct antiglobulin test, notably a cold agglutinin antibody. Once transfusion was safely begun, she was admitted to the PICU.

Dr Coleman, what indications were met for PICU admission in this case?

Dr Nana Coleman, Pediatric Critical Care

The constellation of tachycardia, fever, tachypnea, and painful lymphadenopathy raised concerns for compensated septic shock. Although she remained normotensive and did not meet indications for vasoactive support, she remained tachycardic and ill-appearing even when afebrile. Close monitoring of respiratory status following blood product administration would be key given the total volume of fluid administered during resuscitation and tachypnea noted on arrival. Manifestations of her illness had been rapidly escalating, and the interdisciplinary coordination of the remainder of the diagnostic workup would be optimized in an ICU setting.

How do you approach the diagnostic process and acute management for an ICU patient with an extensive outpatient workup?

Initial stabilization took priority over additional diagnostic measures. She received empirical ceftriaxone and vancomycin for sepsis and completed the CT chest, abdomen, and pelvis. As a general pediatrician trained to recognize and manage critically ill and injured children, an intensivist must examine the diagnostic workup with a fresh perspective and collaboratively integrate the expertise of consulting physicians to ensure a comprehensive approach to testing and care. Despite her negative infectious workup, an immune system dysregulation with subsequent hyperinflammation remained high on the differential, prompting further discussion with ID and rheumatology.

Dr DeGuzman, what aspects in this patient's history and laboratory testing were consistent with an underlying rheumatologic condition?

Dr De Guzman

The key laboratory findings that suggest an autoimmune condition are

TABLE 2 Comparison of Laboratory Values Obtained 2 Weeks Apart at the Initial ED Visit Presentation and the Subsequent Visit That Resulted in ICU Admission

Laboratory Test	First ED Visit	Second ED Visit	Reference Range
Hemoglobin, g/dL	10.6	8.3	10.6–13.4
WBC, cells/μL	3.91	3.25	$4.27–11.4 \times 10^3$
Platelets, cells/μL	239	130	$199–369 \times 10^3$
Ferritin, ng/mL	179	353	10–60
LDH, U/L	1088	612	140–280
D-Dimer, μg/mL	1.14	2.62	<0.40
AST, U/L	25	154	11–28
ALT, U/L	61	61	15–40
SUN, mg/dL	10	23	2–23
Creatinine, mg/dL	0.42	0.30	0.30–0.60

the progressive development of leukopenia, thrombocytopenia, and a cold agglutinin autoimmune hemolytic anemia. The insidious onset of fatigue, fever, oral ulcers, and maculopapular rash in the setting of the aforementioned hematologic laboratory findings fulfill several of the clinical criteria needed for a diagnosis of systemic lupus erythematosus (SLE).[4]

What factors cast doubt on determining a unifying diagnosis? What additional diagnostic tests would be indicated at this point?

Although she had constitutional, mucocutaneous, and hematologic manifestations, she had not developed any evidence of impaired renal function or nephritis. Renal involvement (proteinuria, microscopic hematuria, and/or acute kidney injury) has been identified in nearly 80% of children diagnosed with SLE, with a range of 41% to 53% at onset.[5] Additionally, she had not demonstrated joint involvement, and chest radiograph and point of care ultrasound failed to elicit serositis upon admission, 2 additional physical examination findings that can occur in SLE.

On the basis of the criteria from the European League Against Rheumatism and American College of Rheumatology to confirm a diagnosis of SLE, she would require a positive antinuclear antibody titer before calculating her clinical score, which would be 12 at the time of admission (Fig 1).[4] Anti–double-stranded DNA (anti-dsDNA), anti-Smith antibodies, antiphospholipid antibodies, complement levels, and quantitative immunoglobulins all should be obtained with the next blood draw as well.

In addition, her daily fever for nearly one month along with rising AST, ALT, and ferritin was suggestive of an underlying macrophage activation syndrome (MAS), a dysregulation in the release of proinflammatory cytokines that can rapidly progress and lead to profound morbidity and mortality. MAS can occur secondary to a variety of rheumatologic conditions, systemic infections, or present spontaneously, and the pathophysiology and clinical features closely resemble those of hemophagocytic lymphohistiocytosis. Thus, proceeding with lymph node biopsy to further evaluate neoplastic and infectious etiologies would be appropriate.

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

FIGURE 1
Flowsheet for the diagnosis of SLE, cited from the European League Against Rheumatism and American College of Rheumatology consensus statement in 2019.[4]

Dr Rochat, what infectious causes of progressive lymphadenopathy should be evaluated?

Dr Rochat

The most common infectious causes of bilateral anterior cervical lymphadenopathy would be a reactive process to a variety of viruses. Because her initial testing revealed a

positive CMV IgM, additional testing was needed to evaluate for active infection given her noted laboratory abnormalities: cold agglutinin hemolytic anemia, thrombocytopenia, elevated AST and ALT, all which can be seen in severe disseminated CMV. Additional molecular testing from lymph node biopsy, saliva, and urine were valuable to rule out CMV infection definitively as the underlying cause of her presentation, especially with the developing concerns for MAS.

TABLE 3 Trends in Laboratory Evaluation Throughout Her Illness

Laboratory Test	Day 14	Day 28	Day 35	Reference Range
Hemoglobin, g/dL	10.6	8.3	7.2[a]	10.6–13.4
WBC, cells/μL	3.91	3.25	1.84	4.27–11.4 × 10^3
Platelets, cells/μL	239	130	55	199–369 × 10^3
Ferritin, ng/mL	179	353	2860	10–60
LDH, U/L	1088	612	1000	140–280
D-Dimer, μg/mL	1.14	2.62	3.93	<0.40
AST, U/L	25	154	680	11–28
ALT, U/L	61	61	244	15–40
SUN, mg/dL	10	23	20	2–23
Creatinine, mg/dL	0.42	0.30	0.22	0.30–0.60

Day 14 of symptoms corresponds to the first ED visit, day 28 corresponds with the day of ICU admission, and day 35 corresponds as the last day before definitive diagnosis occurred.
[a] Hemoglobin value obtained one week after transfusion of red blood cells.

Dr Maffei

She underwent excisional biopsy of a left anterior cervical lymph node. While awaiting histopathology results, she developed respiratory distress in the setting of bilateral pleural effusions. She required noninvasive positive pressure ventilation and was started on total parenteral nutrition. Additionally, her mood and behaviors had become erratic, with occasional reports of anger and confusion. Pancytopenia worsened, and ferritin, AST, and ALT rapidly increased (Table 3) over the course of the next week.

Histiocytic necrotizing lymphadenitis was identified on lymph node biopsy without concern for any organisms or neoplastic cells. On the same day her antinuclear antibody panel returned positive, along with positive anti-dsDNA, anti-Smith, and anticardiolipin antibodies (Table 4). With the confirmation of SLE diagnosis, she received 3 days of methylprednisolone and demonstrated initial improvement.

DISCUSSION

Dr Tran, how does a diagnosis of SLE provide context for the findings on lymph node biopsy and the hematologic abnormalities identified before hospitalization?

Dr Tran

Necrotizing lymphocytic histiocytosis identified on pathology report provides additional support for an underlying autoimmune condition. This histologic finding can be seen in Kikuchi-Fujimoto disease, systemic juvenile idiopathic arthritis, and SLE, but the remainder of the laboratory findings provided important clues for the ultimate diagnosis.[7] This patient has an autoimmune hemolytic anemia with low reticulocyte count, which in combination suggests a hyperinflammatory process. Erythropoiesis should increase in response to hemolysis, but many etiologies of systemic inflammation inhibit this process, especially during acute phases of illness.[8] The cold agglutinin identified on antibody screen, named because of the increased activity at temperatures between 0°C and 4°C, can be seen in a variety of autoimmune conditions, including 10% of patients with SLE. This autoantibody targets red blood cells for destruction by the complement system C3 proteins, reducing the total amount of C3 circulating in the serum.[9]

Dr Coleman, how did confirming a diagnosis help guide the subsequent management?

Dr Coleman

Although serum urea nitrogen (SUN), creatinine, and urinalysis initially were normal, awareness of her risk for renal dysfunction played an important role in her existing and future pharmacotherapy. Thus,

TABLE 4 SLE-Specific Antibody Titers, Including Antiphospholipid Antibody Panel

Antiphospholipid antibody panel	Value	Reference Range
Antibody		
SSB	<3.3	<20
Ribonucleoprotein	14.8	<20
Anti-Smith	44.1	<20
SSA Ro52	< 2.3	<20
SSA Ro60	119.4	<20
Scl 70	3.1	<20
Jo1	<2.2	<20
dsDNA	Positive, 1:320	Negative
Antinuclear Antibody	Positive, >1:1280	Negative
Anti-cardiolipin IgM	Positive	22.9 (<12.5)[a]
Anti-cardiolipin IgG	Positive	20.9 (< 15)[a]
Lupus anticoagulant	Negative	Negative
Anti-B2 GPI IgM	Negative	Negative
Anti-B2 GPI IgG	Negative	Negative

GPI, glycoprotein I; Scl, Scleroderma; SS, Sjögrens syndrome.
[a] Titer value (reference range).

vancomycin and cefepime were stopped, because there was low concern for acute bacterial infection.

Close monitoring of hemodynamic parameters, respiratory status, coagulation function, and neurologic status became the key priorities while awaiting the effects of anti-inflammatory therapy. The rising ferritin, AST, and ALT suggested that she had developed MAS and would be at high risk for clinical decompensation. She had already demonstrated thrombocytopenia, altered mental status, and dependence on parenteral nutrition; any additional hepatic involvement could lead to synthetic liver dysfunction, altering coagulation, increasing ammonia production, and impeding glucose metabolism. The most concerning trend, however, was her waxing and waning mental status that pointed to early neurologic involvement of SLE.

Dr Risen, how should neurologic sequelae be monitored in a patient with new diagnosis of SLE?

Dr Sarah Risen, Pediatric Neurology

The neurologic manifestations of SLE may present as a wide spectrum of cognitive, behavioral, sensory, and motor changes, but nearly half of pediatric patients in the acute phase of SLE will develop some degree of neurologic dysfunction.[10] The underlying pathophysiology is multifactorial, and immune mediated alteration of myelin, microvascular thrombosis, and cytokine-induced cerebral inflammation are all suspected to contribute to the neurologic sequelae.[11] Although MRI may reveal white matter changes, cerebral atrophy, and evidence of microthrombi, the lack of a standard pattern on imaging makes screening new patients with SLE less useful. Serial clinical examinations and input from family to observe for changes in behaviors are the key initial parameters to monitor for the cognitive and functional abilities of hospitalized patients with SLE. Changes in attention and school performance serve as common markers of early neurologic dysfunction that may be tracked in an outpatient setting. Unfortunately, the nonspecific nature of inattentiveness and gradual functional decline in SLE frequently leads to missed or delayed identification of neurologic involvement. Given the prevalence of neurologic manifestations in pediatric patients with SLE, formal neurocognitive testing on initial diagnosis may be beneficial for older children and adolescents for whom cooperation with these tests would be developmentally appropriate.

How does the presence of antiphospholipid antibodies alter her risk for serious neurologic complications?

SLE patients with antiphospholipid antibodies are at high risk to develop microvascular and macrovascular thrombotic stroke, the most common thrombotic complication of pediatric SLE.[12] A thorough baseline neurologic examination with interval follow-up is key to the expedient identification of a thrombotic event. Emergent head imaging should occur if a focal change is identified. Additionally, seizures can occur during acute illness because of thrombosis or small vessel vasculitis, because both SLE and the presence of antiphospholipid antibodies independently increase the risk for seizure activity.[13]

Dr Maffei

She developed worsening mood changes with bouts of agitation followed by dysarthria, which warranted urgent evaluation with CT angiography and MRI with stroke protocol. Initial imaging was technically limited; therefore, she required orthodontic evaluation for removal of braces before obtaining complete MRI of the brain and spine (Fig 2). The MRI findings of hyperintensity in the right insular cortex were suggestive of cerebral inflammation associated with SLE. Over the next several days, she developed seizures, had diminishing alertness, and required intubation for airway protection.

Dr Tran, how do you approach anticoagulation for patients with antiphospholipid antibodies?

Dr Tran

Antiphospholipid syndrome (APS) is a proinflammatory and procoagulation state in which microvascular endothelial cells are activated by the presence of antiphospholipid antibodies; however, the benefits of anticoagulation must be carefully weighed against the risks of potential bleeding associated with thrombocytopenia.[14] In this case, the concern for microvascular thrombi in the brain necessitated initiation of therapeutic anticoagulation.

There is a phenotype of APS in which multiple organ systems are involved in progressive

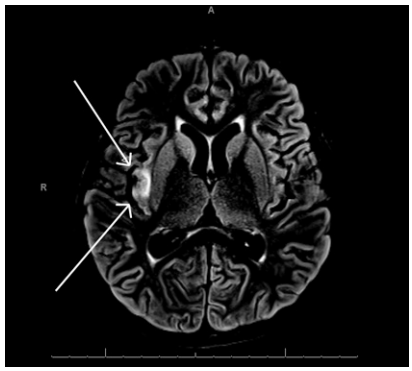

FIGURE 2
Axial T2 MRI brain revealing hyperintensity in the right insular cortex.

microthrombi, known as catastrophic APS, which could be identified with acute change in urine output, mental status, dietary intolerance, or severe pain. The diagnosis requires histologic demonstration of microthrombi, and the treatment would include advanced immunosuppression, immunomodulation with plasmapheresis, and prolonged therapeutic anticoagulation.[15] Given the concern for cerebral microvascular thrombi alone, she did not meet the criteria for catastrophic APS, and the invasive nature of biopsy of the brain outweighed the potential diagnostic benefits.

Dr Maffei

She was started on a continuous heparin infusion and did not develop additional thrombi. After 10 days she was transitioned to subcutaneous enoxaparin to complete at least 3 months of prophylactic anticoagulation. Initiation of antiepileptic medications with levetiracetam and oxcarbazepine prevented additional seizure activity. Given the severity and progressive nature of her SLE, rituximab and cyclophosphamide were added to her induction immunotherapy; hydroxychloroquine was also started before discharge.

During the hospitalization, she had developed nutritional and physical deconditioning, requiring prolonged parenteral nutrition and extensive physical and occupational therapy. She was determined to be an appropriate candidate for inpatient rehabilitation after 4 weeks in the PICU and 6 additional weeks in acute care.

FINAL THOUGHTS

Dr Maffei

The combination of persistent fever along with diffuse cutaneous manifestations with a red facial rash and painless oral ulcerations is a typical initial history for pediatric SLE.[16] Unfortunately, the rash may resemble a viral exanthem or an allergic reaction initially, and the subacute development of constitutional symptoms may occur in a variety of clinical processes.[17]

Dr De Guzman, what epidemiological factors confounded diagnosis in this case?

Dr De Guzman

Diagnosis of SLE before adolescence is uncommon, and the median age of diagnosis for childhood onset SLE is between 11 and 12 years of age: after the onset of puberty. The clinical criteria for diagnosis have not been validated specifically for younger children; however, the limited data describing childhood onset SLE suggest that PICU admission is more common for patients diagnosed before puberty.[16] Despite the relative rarity for prepubescent patients, a general pediatrician's high suspicion for SLE in the appropriate clinical context may hasten diagnosis and limit the morbidity and mortality associated with cumulative inflammation, organ damage, and risk of infection.[18]

Dr Maffei

This case highlights some of the challenges of seeking medical care during the coronavirus disease 2019 pandemic, especially for commonly encountered pediatric symptoms such as fever. The implementation of waivers by the Centers for Medicare and Medicaid Services provided improved reimbursement for telemedicine services, and the US Coronavirus Aid, Relief, and Economic Security Act allowed health care providers to conduct telemedicine visits from home in March 2020.[19] These changes resulted in an exponential increase in the amount of pediatric outpatient visits completed via telemedicine, which was gradually balanced as clinics developed policies to address safety measures for patients and employees.[20] The process for many pediatric clinics has been to require an initial telemedicine visit to evaluate fever, cough, or other symptoms that could be concerning for SARS-CoV-2 infection. Although the goal of such protocols is to mitigate the risk of viral spread in the ambulatory setting, there have been case reports of delayed diagnosis of a variety of acute pediatric diagnoses.[21]

Although video technology has advanced to allow practitioners to complete a limited virtual examination with the assistance of parents and caregivers, finer details of an in-person skin assessment, improved visualization of the oropharynx, and palpation of lymph nodes provide diagnostic clues to differentiate SLE from other causes of persistent fever in children. In this case, the family and PCP remained in communication and coordinated the appropriate follow-up to facilitate expedient diagnosis and initial treatment. Additionally, the majority of her follow-up appointments have been conducted via telemedicine, highlighting a potential improvement in the monitoring of chronic conditions in pediatric neurology and rheumatology, 2 subspecialties traditionally with difficult access to clinic visits for many patients. The option for telemedicine visits as a method to triage acute illnesses for pediatric patients provides convenience for both providers and families, and this case demonstrates how the virtual health care visit can be an appropriate tool to identify acute illness and to escalate treatment to the clinic or even to the ICU.

ABBREVIATIONS

ALT: alanine aminotransferase
APS: antiphospholipid syndrome
AST: aspartate aminotransferase
CMV: cytomegalovirus
CT: computed tomography
ED: emergency department
ID: infectious disease
IgG: immunoglobulin G
IgM: immunoglobulin M
LDH: lactate dehydrogenase
MAS: macrophage activation syndrome
MIS-C: multisystem inflammatory syndrome in children
PCP: primary care pediatrician
PCR: polymerase chain reaction
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
SLE: systemic lupus erythematosus
SUN: serum urea nitrogen
WBC: white blood cell count

REFERENCES

1. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 2. *Arthritis Rheumatol.* 2021;73(4):e13–e29
2. Sood AK, Sachdeva A. Rickettsioses in children - a review. *Indian J Pediatr.* 2020;87(11):930–936
3. Chow A, Robinson JL. Fever of unknown origin in children: a systematic review. *World J Pediatr.* 2011;7(1):5–10
4. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol.* 2019;71(9):1400–1412
5. Brunner HI, Gladman DD, Ibañez D, Urowitz MD, Silverman ED. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. *Arthritis Rheum.* 2008;58(2):556–562
6. Parodi A, Davì S, Pringe AB, et al; Lupus Working Group of the Paediatric Rheumatology European Society. Macrophage activation syndrome in juvenile systemic lupus erythematosus: a multinational multicenter study of thirty-eight patients. *Arthritis Rheum.* 2009;60(11):3388–3399
7. Hutchinson CB, Wang E. Kikuchi-Fujimoto disease. *Arch Pathol Lab Med.* 2010; 134(2):289–293
8. Bashal F. Hematological disorders in patients with systemic lupus erythematosus. *Open Rheumatol J.* 2013;7:87–95
9. Jäger U, Barcellini W, Broome CM, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting. *Blood Rev.* 2020;41(1): 100648
10. Alessi H, Dutra LA, Braga P, et al. Neuropsychiatric Lupus in clinical practice. *Arq Neuropsiquiatr.* 2016;74(12):1021–1030
11. Muscal E, Brey RL. Neurologic manifestations of systemic lupus erythematosus in children and adults. *Neurol Clin.* 2010; 28(1):61–73
12. Sciascia S, Sanna G, Khamashta MA, et al; APS Action. The estimated frequency of antiphospholipid antibodies in young adults with cerebrovascular events: a systematic review. *Ann Rheum Dis.* 2015;74(11):2028–2033
13. Noureldine MH, Harifi G, Berjawi A, et al. Hughes syndrome and epilepsy: when to test for antiphospholipid antibodies? *Lupus.* 2016;25(13):1397–1411
14. Muscal E, Brey RL. Antiphospholipid syndrome and the brain in pediatric and adult patients. *Lupus.* 2010;19(4):406–411
15. Madison JA, Zuo Y, Knight JS. Pediatric antiphospholipid syndrome. *Eur J Rheumatol.* 2019;7(suppl 1):1–10
16. Harry O, Yasin S, Brunner H. Childhood-onset systemic lupus erythematosus: a review and update. *J Pediatr.* 2018;196: 22–30.e2
17. Caeiro F, Michielson FM, Bernstein R, Hughes GR, Ansell BM. Systemic lupus erythematosus in childhood. *Ann Rheum Dis.* 1981;40(4):325–331
18. Hui-Yuen JS, Imundo LF, Avitabile C, Kahn PJ, Eichenfield AH, Levy DM. Early versus later onset childhood-onset systemic lupus erythematosus: clinical features, treatment and outcome. *Lupus.* 2011;20(9):952–959
19. Koonin LM, Hoots B, Tsang CA, et al. Trends in the use of telehealth during the emergence of the COVID-19 pandemic — United States, January-March 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(43):1595–1599
20. Howie, F, Kreofsky, BL, Ravi, A, Lokken T, Hoff MD, Fang JL. Rapid rise of pediatric telehealth during COVID-19 in a large multispecialty health system [published online ahead of print May 17, 2021]. *Telemed J E Health.* doi:10.1089/tmj.2020.0562
21. Rosenberg Danziger C, Krause I, Scheuerman O, et al. Pediatrician, watch out for corona-phobia. *Eur J Pediatr.* 2021;180(1):201–206