

TEACHING FILES (GRAND ROUNDS)

FEVER AND RASH, NOT ALWAYS VIRAL EXANTHEM

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Clinical Problem:

A 7 years old previously healthy female presented to the emergency department for facial and truncal rash, facial swelling, and fever to 102°F which started 2 weeks prior. Patient also reported sore throat, pain in her back, knee, abdomen, decreased appetite, and vomiting. Mother denies any new food, lotions, or medications. Patient lives in the United States but does travel to Tijuana, Mexico. She was seen at a clinic in Mexico during first week of symptoms and given 2 doses of dexamethasone injection intramuscular 48 hours apart and ceftriaxone injection intramuscular for 3 consecutive days for a presumed throat infection. No throat cultures were obtained. Throat pain improved after the medications but her rash worsened. There were no upper respiratory tract symptoms, chest pain, diarrhea, dysuria, eye or tongue redness, or swelling to extremities. On presentation to us, temperature was 37.3°C, heart rate 128 beats/minute, respiratory rate 22 breaths/minute, blood pressure 121/77 mm Hg, oxygen 100% on room air. On examination, she had mild diffuse facial edema, hyperemic and edematous gums, posterior palate erythematous ulcers (Fig. 1A), generalized abdominal tenderness, diffuse paraspinal and midline lumbar tenderness and a confluent erythematous macular rash to face and chest (Fig. 1B, C). Investigations revealed negative rapid streptococcal antigen test, negative monospot test, normal C-reactive protein (CRP) 0.8 mg/dl and ESR 6 mm at end of 1 hour. Serum sodium was 132 mmol/L, potassium 4.6 mmol/L, chloride 98 mmol/L, pCO₂ 22 mmol/L, BUN 11 mg/dL, creatinine 0.37 mg/dL, glucose 106 mg/dL, calcium 8.7 mg/dL, alkaline phosphatase 282 IU/L, albumin 3.3 g/dL, total protein 6.8 g/dL, total bilirubin 1.1 mg/dL, AST 650 IU/L, and ALT 227 IU/L. Complete blood count revealed white blood cells (WBC) 9900 cells/cumm, hemoglobin 15.4 g/dL, hematocrit 46.2%, MCV 89.7fL, MCH 29.8pg, MCHC 33.3%, RDW 14.5 Unit, platelets 63,000 cells/cumm. Consultations from dermatology, infectious disease, ophthalmology, and rheumatology were obtained.

Additional investigations revealed elevated creatine kinase (CK) 2011 U/L, lactate dehydrogenase (LDH) 1567 U/L, ferritin 605 ng/mL (Normal 6-70 ng/mL), and C3 complement 125 mg/dL (Normal 70-124 mg/dL). C4 was decreased at 14 mg/dL (Normal 20-42 mg/dL). Infectious work up was negative for serum enterovirus PCR, herpes simplex virus 1,2 PCR, hepatitis A, B, C and E Elisa and antistreptolysin O <25 IU/mL. Blood culture did not grow any organism. Mycoplasma IgM, Epstein-Barr virus VCA IgM, cytomegalovirus IgM, herpes simplex virus 6 IgM, and dengue IgM were also negative. Rheumatology work up was negative for ANA, p and c-antineutrophilic cytoplasmic antibody (ANCA), smith antibody, antiphospholipid IgG and

Figure 1. Oral ulcers (A) and macular rash to face (B) and trunk (C)

Figure 1 (A)



Figure 1 (B)



Figure 1 (C)



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IgM, ds DNA, but positive for ribonucleoprotein (RNP) antibody [5.8AI (Normal <1 AI0) and aldolase [28.4 U/L (Normal 3.4-8.6 U/L)]. She had progression of edema evolving into extremity and truncal edema associated with myalgias. She was started on intravenous (IV) methyl prednisolone (15 mg every 6 hours) with improvement in her symptoms and was discharged home on oral prednisolone (15 mg every 8 hours). On follow up with rheumatology, she subsequently re-developed weakness with myalgias, diffuse tissue edema, persistent hard palate ulcers, and a more classic malar type rash upon slow wean of steroids. RNP remained persistently elevated. Patient is followed by rheumatology with additional flares requiring higher dose steroids in addition to mycophenolate mofetil and hydroxychloroquine.

What is the likely diagnosis?

Discussion:

Mixed connective tissue disorder (MCTD) given her elevated RNP and heterogeneous symptom presentation. MCTD has overlapping manifestations of systemic lupus erythematosus (SLE), systemic sclerosis, inflammatory myositis, and arthritis, in addition to high autoantibodies to RNP.¹ Some rheumatologists view MCTD as an undifferentiated connective tissue disease or overlap syndrome, while others classify it as a separate disease.² The pediatric median age of onset is 11 years (range from 2-16 years).³ About 80% of patients are female, and many will evolve into systemic sclerosis or lupus as they get older.⁴ There are different classifications for MCTD, and the Alarcon-Segovia criteria are one of the easiest to apply in the clinical setting.⁵ These classification criteria have been evaluated for adult but not pediatric MCTD and are usually used not for diagnostic purposes, rather for research and tracking. One common requirement in all criteria is high titer anti-RNP antibodies.⁶ Other rheumatic diseases can have high anti-RNP antibodies and in SLE it can be a marker for more severe disease. Anti-RNP is detectable in 25-47% of SLE patients usually in conjunction with anti-Smith antibodies, but high titers of isolated anti-RNP antibodies are diagnostic of MCTD.^{4,7}

Most common findings in MCTD include Raynaud's phenomenon, swollen hands, arthritis, sicca complaints, and esophageal disease. Raynaud's phenomenon may present years before other findings, and any pre-pubertal child who develops this should be assessed for rheumatologic disease.⁴ Other manifestations are lupus-like and or scleroderma skin changes, myositis, serositis, and lung disease. Our patient had a primary facial and truncal rash, facial swelling, and back pain. She also had oral ulcers which are not included in MCTD criteria but demonstrate potential overlap features with SLE. Case reports have described patients presenting with oral ulcers at the time of MCTD diagnosis.^{8,9} Prior treatment with corticosteroids may have also altered her symptoms and presentation.

MCTD can be one of the milder rheumatic diseases but the prognosis is primarily dependent on the predominating disease entity it may follow. Of those with more of systemic sclerosis or SLE pattern, one third can develop serious lung disease. Pulmonary

dysfunction may be underestimated in pediatric patients due to insidious onset.¹⁰ Treatment for MCTD is targeted for organ involvement. Vasodilators can be used for Raynaud's phenomenon, proton pump inhibitors for gastroesophageal reflux, and topical steroids for inflammatory rashes. NSAIDs or antimalarials are recommended for mild disease while corticosteroids and other immunosuppressants may be required for moderate to severe disease.⁴

While rheumatologic disorders are not very common in the pediatric population, they should be considered when the presenting symptoms are prolonged for typical viral illnesses or laboratory studies are concerning for an inflammatory process. The persistently elevated anti-RNP antibodies and her improvement with steroids ultimately led to her diagnosis of MCTD.

Compliance with ethical standards

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Conflict of Interest: None

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