## APPENDIX MATERIAL

### The Socrates Project for Difficult Diagnosis at Northwestern Medicine

Benjamin D. Singer, MD, Alexandra M. Goodwin, MD, Anand A. Patel, MD, and Douglas E. Vaughan, MD

### Sample Socrates Project Documentation

This is a 38-year-old woman in the intensive care unit with the following problem list. We are asked to comment on a unifying diagnosis for her unexplained shock and multi-organ dysfunction syndrome.

1) Shock, type IV respiratory failure, multi-organ dysfunction syndrome
2) Viral prodrome with rhinovirus/enterovirus respiratory infection diagnosed by multiplex PCR of BAL fluid; took course of azithromycin
3) Leukocytosis/leukemoid reaction with neutrophilia and shift toward immaturity
4) Lymphadenopathy in multiple chains (at least cervical, axillary, mediastinal, and inguinal)
5) Hepatosplenomegaly
6) Thrombocytopenia, suspected to be immune-mediated with decreased production
7) Normocytic anemia
8) Cutaneous purpura
9) AKI without proteinuria
10) No acute response to high-dose steroids; receiving IVIg

The differential diagnosis includes:

1) Sepsis from occult infection with broad possibilities – fungal, mycobacterial, viral, bacterial
2) Atypical presentation of an aggressive cancer or lymphoproliferative disorder – angiotropic lymphoma, which is notoriously difficult to diagnose pre-mortem, has been reported to present with distributive shock and multi-organ failure. Also consider idiopathic multi-centric Castleman Disease with excess interleukin-6 leading to shock and multi-organ dysfunction.
3) Auto-inflammatory/auto-immune disorder – Adult Onset Still's Disease is challenging to diagnose in this setting but should respond to steroids and IVIg; not classic for Kikuchi or Kimura syndrome but a lymph node biopsy would help clarify; not clearly a genetic auto-inflammatory disorder (FMF, CPAS, TRAPS, HIDS, etc.) without lengthy preceding episodic course of fever, abdominal pain, or other subacute/chronic symptoms and negative family history

4) Vasculitis is on the differential but less likely with strikingly negative serologies, no proteinuria or otherwise active urinary sediment, no response to steroids; would need a very specific test (i.e., obvious biopsy findings) to make this diagnosis
5) Hemophagocytic lymphohistiocytosis with incomplete features – even if we invoke HLH-like physiology, it would be secondary and we would still need to find primary driver (could it be an unusual immune reaction to the viral pathogens already identified?)

We recommend:

1) Send shotgun DNA or 16S ribosomal RNA gene metagenomic testing from the blood – this is a test for pathogen identification that does not require specifying a suspected pathogen; extensive other infectious testing is pending
2) Send adenovirus, Coxiella (Q fever), leptospira, bartonella, brucella PCRs and serologies from blood (all with low pre-test probability but some require alternative antibiotic regimens if positive)
3) Await results of lymph node (if able, excisional) and skin biopsy to evaluate for vasculitis, ? angiotropic lymphoma (note some reports of higher biopsy yield if a hemangioma is biopsied)
4) Bone marrow final studies pending
5) TEE as planned
6) Send NK activity panel to support HLH-like physiology, although the primary driver needs to be identified as above
7) IgE level (eval for Kimura syndrome, but low pre-test probability)
8) HHV-8, IL-6 and VEGF levels (elevated in Castleman Disease)
9) PET-CT when stable to evaluate for focus amenable to biopsy
10) Liver biopsy can be helpful in fever/inflammation of unknown origin (mostly to find granulomas) but is currently precluded by procedural bleeding risk
11) Consider genetic testing for auto-inflammatory syndromes if above negative; could also consider empiric trial of colchicine if evaluation otherwise negative