tions, recurrent upper and lower respiratory tract infections, and neutropenia. The younger sister had repeated oral infections that ultimately resulted in development of oral strictures. A twin sister of the younger child who had a similar presentation died at age 3 years from a septic event.
Objective: To characterize the functional responses of patient neutrophils as a way to identify the underlying immunodeficiency.
Methods and Results: Neutrophils from both sisters exhibited normal O2- production to phorbol myristate, fMLF, and cytochalasin B + zymosan. Although degranulation and staphylocidal activity were not dramatically altered, a profound chemotactic defect in vitro was detected. Microscopic examination of purified neutrophils from both sisters showed abnormal nuclear morphology in 40-50% of the cells with herniation of nuclear lobes into plasma membrane-enclosed surface blebs. No abnormal morphology was observed in the neutrophils on routine peripheral blood smears. Electron microscopic examination of isolated cells confirmed abnormal morphology in both neutrophils and eosinophils. Moreover, herniation of nuclear lobes coincided with retraction of the granules into the central region of the cells, resulting in an agranular region in the periphery of the cell. Confocal microscopy, using Alexa Fluor 546-phalloidin to identify filamentous actin and DAPI to localize nuclei, showed that cells with herniated nuclear lobes exhibited increased levels of filamentous actin compared to either patient cells with normal nuclear lobes or to normal neutrophils.
Conclusion: Abnormal nuclear morphology, profound chemotactic defect, and cytoskeletal anomaly in these two sisters with recurrent infections represents a novel defect of neutrophils that is likely autosomal recessive.
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A Novel Autosomal-dominant Late-onset Immunodeficiency with Susceptibility to Mycobacteria, Fungi, Papillomavirus and Myeloid Malignancies

Donald Vinh, Smita Patel, Gulbu Uzel, Victoria Anderson, Alexandra Freeman, Kenneth Olivier, Houda Elloumi, Li Ding, Douglas Kuhns, Danielle Fink, Deborah Long-Priel, Frank DeLeo, Elizabeth Sampaio, Michelle Paulson, Amy Hsu, Adrian Zelazny, Jeremy Root, David Frucht, Steven Holland. *National Institutes of Health (NIH) National Institute of Allergy & Infectious Diseases Laboratory of Clinical Infectious Diseases Bethesda, USA*

Background: Primary immunodeficiencies characterized by selective predisposition to non-tuberculous mycobacteria (NTM) disease include autosomal dominant and recessive disorders of the IL-12/IL-23/IFN-γ axis including STAT1, and X-linked recessive defects in NFκB-essential modulator (NEMO). In the process of evaluating patients with disseminated NTM infections, we encountered a discrete group of patients whose clinical course, laboratory features, and family histories indicate a novel immunodeficiency.
Materials/Methods: We identified patients with severe NTM infection, for whom mutations in the genes of the IL-12/IL-23/IFN-gamma axis were excluded by function or sequence or both. We also reviewed the medical charts of relevant family members.
Results: 14 patients were evaluated at the NIH and 9 affected family members were identified (table). HIV was negative. This novel syndrome is vertically transmitted, suggesting autosomal dominance. The syndrome was identified by susceptibility to NTM infections. It is characterized by profound circulating monocytopenia, and B and NK lymphocytopenia. HPV infection was common (n=13) and severe with several cases of progression to neoplasia; individual cases had severe EBV or VZV. Invasive fungal infections occurred primarily with moulds (4 with *Aspergillus spp*. or its teleomorph, *Neosartorya spp*.), although 1 case involved *C .neoformans* and 2 patients had disseminated *histoplasmosis*. Four patients developed pulmonary alveolar proteinosis (PAP), a disorder of excessive lipoproteinaceous material within alveoli, but they did not have mutations in the GM-CSF receptor or detectable autoantibodies to GM-CSF. Nine cases progressed to myelodysplastic syndrome or leukemia, 1 developed aplastic anemia, and 5 developed clonal proliferation of large granular lymphocytes. Of the 23 cases, 11 (47.8%) are deceased.
Conclusions: This novel autosomal dominant immunodeficiency syndrome is characterized by profound circulating monocytopenia and adult-onset mycobacterial disease. Infectious susceptibility extends to viruses, especially HPV, and to moulds. Development of PAP, progression to myelodysplasia, and high mortality suggest early definitive intervention such as bone marrow transplantation is warranted.

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Idiopathic CD4+ Lymphocytopenia: Natural History and Prognostic Factors.

Dimitrios Zonios, Judith Falloon, John Bennett, Pamela Shaw, Doreen Chaitt, Michael Polis, Joseph Kovacs, Richard Davey, H. Clifford Lane, Henry Masur, Irini Sereti. *Laboratory of Clinical Infectious Diseases and Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA*

Background: Idiopathic CD4 lymphocytopenia (ICL) is a rare non-HIV related syndrome first defined in 1992 as an absolute CD4 T lymphocyte count of less than 300 cells/mm^3 or of less than 20% of total T cells on more than one occasion and the absence of any defined immunodeficiency or therapy associated with low CD4 T cells. It is a rare, heterogenous syndrome not caused by HIV-1 or 2, HTLV-I or II or other transmissible agent.
Objectives: The clinical course, immunologic characteristics, CD4 T cell kinetics, long-term outcome and prognosis of this syndrome have not been studied adequately.
Materials and Methods: Patients with ICL were enrolled between 1992 and 2006 in a NIH coordinated prospective natural history clinical study. This included clinical assessment, history, immunologic and virologic investigation while the patients were followed at least annually.
Results: Thirty-nine patients (17 men, 22 women), 25 to 85 years old with ICL were evaluated and thirty-six were followed for a median of 49.5 months (range). Most of the patients presented with cryptococcal and non-tuberculous mycobacterial infections, while seven patients presented with no infection (incidental finding of low CD4 T cell count). In thirty-two, CD4 T cell counts remained below 300/mm^3 during the entire study period without progression of lymphopenia and in seven normalized after an average of 31 months. Using a linear mixed model approach to fit the individual CD4 trajectories, the CD4 velocity was estimated at 0.66/mm^3/month (95% CI: -0.20, 1.54) and was not significantly different from zero (p=0.13). Overall, fifteen patients (41.6%) developed an opportunistic infection in follow up (mostly HPV, VZV infections and candidiasis), five (13.8%) of which were AIDS defining clinical conditions, and four patients (11.1%) developed autoimmune diseases. Patients without opportunistic infections (OIs) at presentation remained asymptomatic. Seven patients died, four from ICL related opportunistic infections within 42 months of diagnosis. CD8 T lymphocytopenia ($<$180/mm^3) and high CD4 T cell activation (measured by HLA-DR expression) at presentation were associated with adverse outcome (ICL related death) (p=0.003 and 0.02 respectively).
Conclusions: ICL is a heterogeneous yet distinctive, clinically and immunologically, from HIV infection condition. CD4 T cell counts in ICL remain stable or improve in the majority of patients but life-threatening OIs and autoimmune diseases can occur.