Non-tuberculous mycobacterial infections in hematology-oncology: we need to look harder

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In the current issue, Tsumura *et al.* report on the incidence of non-tuberculous mycobacterial diseases (NTM) in Japanese children followed in hematology / oncology departments between 2010 and 2020.[1] While the typical NTM infection in childhood is isolated painless cervical lymphadenopathy in immunologically normal children, there are other NTM infections that present with disseminated or severe manifestations, which are often compounded by delay in diagnosis, contributing to morbidity, if not mortality. Unfortunately, in most microbiology laboratories, the ordering physician needs to specify mycobacterial culture in order to recover NTM. The same applies to respiratory samples, which require specific mycobacterial staining and culture conditions. Even as we move more aggressively into the world of molecular diagnosis and characterization of infecting organisms, the standard molecular tests for mycobacteria cover only a small number of the expanding world of NTM, which now number over 200 species. So, the point is: to find NTM you have to look for them and you have to be active in their pursuit. Since NTM are in most water, air and dirt, their opportunities to infect vulnerable patients are almost boundless.

This is where the current paper is helpful. The 36 patients Tsumura *et al.* identified had hematologic malignancies, developed infection following hematopoietic stem cell transplantation (HSCT), or had inborn errors of immunity (IEI). This is an important undertaking, as the incidence and prevalence of NTM infections are changing markedly in industrialized countries, and now exceed the rates of tuberculosis in the US and elsewhere.[2,3] The implications of this change in epidemiology are slowly becoming apparent, but at a minimum, they mean that we need to increase our awareness of and screening for these infections in our vulnerable populations; that is, we need to be sure to specifically culture blood and sputum for NTM rather than only routine infections. Tsumura *et al*. estimated the incidence of NTM in pediatric hematologic malignancies at 0.27%, whereas the rate in pediatric HSCT recipients was 0.83%. Interestingly, the highest rates of infection were seen in the lung in those with pulmonary graft-*versus*-host disease (GvHD), and were predominated by the rapid growing mycobacterium (RGM) *M. abscessus*, followed by the slow growing mycobacterium (SGM) *M. avium* complex. The good news is that these infections were not direct causes of death in their series, as survival was determined by the underlying illness and treatment, e.g., acute lymphoblastic leukemia, HSCT. However, the treatments for these infections are difficult, toxic and prolonged. And they do not make anything better.

What are the mechanisms that these important observations suggest? NTM infections are uncommon complications of cancer and HSCT, which suggests that subtle genetic or acquired predispositions are being uncovered by the stress of treatment or transplant, rather than just being “bad luck”. The finding that the rate of NTM in pulmonary GvHD approaches 5% is surprising. The authors rightly discuss cystic fibrosis, a disease characterized by bronchiectasis and inflammation and often complicated by NTM infection. However, the high rates of NTM in the lung in pulmonary GvHD raise the possibility that the host-directed inflammation itself might be driving the epithelial damage and susceptibility. Similar pathophysiology has been described in the syndrome of autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED).[4] In that condition, activated T cells infiltrate the oral mucosa where they produce high levels of IFNγ, which in turn leads to epithelial disruption and *Candida* invasion; control of the inflammation itself controls the *Candida*.[4] Similar findings have been reported in a STAT1 gain of function (GOF) disease mouse model, where control of the IFNγ-mediated inflammation can control *Candida*.[5] These findings may also explain the success of ruxolitinib in human STAT1 GOF disease.[6] Is the pulmonary GvHD / NTM association a similar pathophysiology, with local inflammation leading to

epithelial disruption? Review of biopsies for IFNγ expression or downstream targets should help clarify this.

What about anticytokine autoantibodies against IFNγ or IL23 (well-described causes of mycobacterial infection) being elaborated post-HSCT and predisposing to NTM? We will have to look to know.[7] Finally, the use of genetics in the diagnosis of leukemia and other hematologic malignancies is now routine. However, those same genetic tools to look for infection risk post-HSCT have not been applied as robustly. But they should be! For instance, the common *CLEC7A* (DECTIN-1) mutation Y238X predisposes to invasive *Aspergillus* whether derived from the HSCT donor or recipient.[8] These same *CLEC7A* mutations drive susceptibility to *Coccidioides* infection, but are only evident when people travel to endemic regions.[9] These uncommon (but not so rare) NTM infections offer an important opportunity to sort out innate and acquired predisposition, which will help us develop prophylaxis and therapy. Tsumura *et al*. have given us important new information that helps frame the importance of the search for NTM infections, their associations with severe complications of HSCT, and will help us determine underlying causes. But if we want to find, we must look, and we must look harder than we have in the past.

Disclosures

No conflicts of interest to disclose.

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