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Once again, rare diseases provide a spotlight

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This year's Academy Award winner, the film *Spotlight*, details the success of a small, focused investigative research team in uncovering a pattern of abuse of children by Catholic priests and the cover-up that took place across the U.S. The *Spotlight* team, by following what had originally appeared to be a few isolated cases, opened up a floodgate which ultimately exposed a nationwide scandal.

A longitudinal focused investigation into a phenomenon that initially appears to be sporadic sometimes provides a spotlight illuminating paths that were not previously appreciated.

For some time now it has been observed that patients with the rare autosomal recessive disorder Gaucher disease are at increased risk of developing multiple myeloma and monoclonal gammopathy of undetermined significance (MGUS) [1–3], disorders characterized by the clonal expansion of transformed plasma cells. However the reason for this association was not well understood. In a recent Brief Report published in the February 11th issue of the *New England Journal of Medicine*, Nair et al. [4] used the concurrence of Gaucher disease and multiple myeloma to probe the potential role of glycolipids in myeloma pathogenesis.

This study grew out of two previous discoveries by the authors. The first was the recognition of lysophosphatidylcholine (LPC)-reactive natural killer T cells in patients with multiple myeloma, which was an early indication that lipid-reactive type II NKT cells may contribute to the progression of B cell malignancies [5]. The second was the recognition of LGL1-reactive type II NKT cells in both patients with Gaucher disease and a murine model with myeloid-restricted glucocerebrosidase deficiency [6]. These LGL1-reactive NKT demonstrated a follicular helper T cell phenotype and were able to provide help to B cells in vivo and in vitro. With these two findings, the authors became intrigued with the possibility that chronic stimulation of B cells by these lipid antigens was driving the development MGUS and multiple myeloma. Evaluating patient samples by serum protein electrophoresis and blotting onto lysolipid-saturated membranes, they found that 7 of 9 patients with

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Gaucher disease and monoclonal gammopathy (78%) and 10 of 11 patients with polyclonal gammopathy (91%) showed reactivity between their immunoglobulins and the lysolipid LGL1. They did not find similar reactivity in 5 patients with Gaucher disease who had normal immunoglobulins, 10 patients with polyclonal gammopathy without Gaucher disease or 25 healthy donors. Similarly, in their Gaucher mouse model, after injecting mice intraperitoneally with LGL1, they observed lysolipid reactivity in 6 of 6 mice (100%) while there was no reactivity in 10 control mice. Furthermore, evaluating samples from patients with sporadic monoclonal gammopathy without Gaucher disease, they noted that 5 of 16 patients with MGUS alone (31%) and 17 of 50 patients with myeloma (34%) showed immunoglobulin reactivity against the lysolipid. The lipid reactivity was validated with several different approaches including ELISA assays and the use of sphingosine-coated beads.

These findings are quite exciting for the oncology field. This is the first etiologic evidence for specific causal underlying antigenic reactivity of clonal immunoglobulin, and could be operative in as many as a third of cases even of non-Gaucher-associated myeloma. Moreover, it suggests potential new strategies to prevent progression from MGUS to myeloma, or to treat such cancers by targeting the underlying antigen.

The authors of the study suggest that in subjects with Gaucher disease and LGL1-associated gammopathy, substrate reduction therapy with a drug that inhibits glucosylceramide synthase such as eliglucerase may provide targeted protection [7]. They showed that feeding eliglucerase to glucocerebrosidase-deficient mice who had clonal immunoglobulins led to a reduction in anti-LGL1 antibodies, as well as a reduction of clonal antibodies in vivo, and speculated that this strategy may also be effective in human patients [4].

However, the vast majority of patients with Gaucher disease do not develop multiple myeloma or even MGUS [3,8,9]. Thus other factors likely contribute to the evolution of the malignancy in a subgroup of patients. Eliglucerase therapy is not entirely benign, and it can cost up to several hundreds of thousands of dollars per patient per year. Furthermore, enzyme replacement therapy, the current standard therapy for Gaucher disease, has a significant impact on plasma LGL1 levels [9], and has been shown to reduce hypergammaglobulinemia in affected patients [10]. Thus advocating for administration of eliglucerase as a protective measure in patients with MGUS without Gaucher disease or even Gaucher disease without MGUS is likely premature. As the authors concede, further studies confirming these findings and better defining the contribution of bioactive lipids to myeloma are certainly necessary.

In recent years the boundaries between Mendelian and complex disorders have become increasingly blurred. There are now examples of heterozygosity for one disorder serving as a risk factor for another [11]. The Gaucher field has already provided a prior example, namely, patients with glucocerebrosidase mutations have a much higher risk of parkinsonism, directing research towards exploring the role of lysosomal dysfunction in neurodegeneration [12,13]. The current report provides a second example of mutations in one gene leading to a metabolic perturbation predisposing patients to yet another potentially lethal disorder.

The current paper is yet another example of how the study of a rare disorder can provide a beacon, leading researchers to insights that can impact a far broader population. The astute clinical observation that some patients with Gaucher disease go on to develop MGUS or multiple myeloma provided the necessary spotlight on lysolipids, leading to the recognition of their contribution to the etiology of multiple myeloma. As we carefully phenotype our patients with Mendelian disease, we are likely to illuminate many such paths worth pursuing.

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