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IgD and IgE Variants of Myeloma: Valuable Insights and Therapeutic Opportunities

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Multiple myeloma (MM) is a neoplastic proliferation of monoclonal plasma cells associated with a serum and/or urine monoclonal (M) protein and clinical manifestations of renal dysfunction, anemia, hypercalcemia, and lytic bone lesions.[1] It accounts for approximately 13% of hematologic malignancies.[2-4] Immunoglobulin G (IgG) MM, immunoglobulin A (IgA) MM, and light chain myeloma account for approximately 90% of all myeloma cases; the remainder consist of immunoglobulin M (IgM), non-secretory, immunoglobulin D (IgD), and immunoglobulin E (IgE) subtypes.[5] IgD MM accounts for approximately 2% of all myeloma cases.[3,6]

As described in the excellent review by Drs. Pandey and Kyle in this issue of ONCOLOGY, IgD MM is characterized by detection of small levels of M-protein on serum protein electrophoresis, as well as a lambda light chain predilection.[3] These patients typically present with advanced-stage disease at diagnosis, and often with extramedullary disease (EMD). IgE myeloma is even less common, with approximately 50 cases reported in the literature, and is characterized by a small M-protein level but otherwise typical features, such as bone pain, anemia, renal failure, hypercalcemia, and Bence Jones proteinuria. It is often associated with secondary amyloid light chain (AL) amyloidosis, and there appears to be an increased incidence of plasma cell leukemia (PCL) as well.[4] Importantly, a hallmark of IgE myeloma is t(11;14)(q13;q32).[4]

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As noted by Drs. Pandey and Kyle, IgD and IgE levels are generally low and hence not readily detected; therefore, patients in whom protein electrophoresis detected only free monoclonal light chain immunoglobulin should also be screened for the presence of both IgD and IgE.[3,4] In the context of serum protein electrophoretic assessment, it is important to remember that IgD quantifiably is measured in the range of 0 to 10 mg/dL, while IgE is only present at trace levels. Thus, in both IgD MM and IgE MM, there may be a smaller, unrecognizable M-spike on electrophoresis, and the authors appropriately emphasize that this may lead to diagnostic errors in recognizing these patients.[3]

Interestingly, the normal counterpart of IgD MM cells in germinal centers display extensively mutated *IgVH* genes, switching of the mu constant region and delta constant region (Cmu-Cdelta), and lambda light chain expression.[7] Translocation (11;14)(q13;q32) is a hallmark not only of IgE MM, but also of IgM and non-secretory myeloma variants.[6] IgD MM typically involves younger patients, with a median age of 52 to 60 years at onset, a predilection for male gender, and a generally shorter survival time.[3] Another feature emphasized in the review by Pandey and Kyle is the detection of advanced disease at the time of diagnosis.[8,9] An additional important prognostic feature is the presence of EMD; extramedullary plasmacytoma is reported to occur in 13% to 19% of myeloma patients,[10-12] with the prevalence of EMD in IgD MM being significantly higher, ranging from 20% to 60%.[9] Various studies have clearly described shortened progression-free survival time for patients with EMD.[13] In an important series of 53 cases of IgD MM by Bladé et al, extramedullary involvement was found in 19% of patients and manifested by hepatomegaly, splenomegaly, and lymphadenopathy, with a further 15% developing EMD later in the course of their disease.[9] In this same series, up to 19% of patients had systemic amyloidosis, and both cardiac and renal involvement were seen. Unsurprisingly, outcomes for patients with amyloid involvement proved inferior to those without amyloidosis, but they were not meaningfully different from outcomes seen with other isotypic forms of myeloma and associated amyloidosis.[10] While it is commonly accepted that IgD amyloidosis is a distinct entity,[10] recent studies have identified that t(11;14) in this disease group is associated with poorer outcome and shorter survival time.[11] Drs. Pandey and Kyle also outline the relatively high frequency of PCL in patients with IgD MM, albeit lower than in IgE MM, and both as a primary, as well as a secondary, phenomenon. The prognosis in the latter group, concordant with other isotypes, is especially poor.

Pertinent laboratory values in IgD MM include a bias for lambda light chain expression, with a reversed kappa:lambda light chain ratio. These range from 60% to 90%, depending on the series.[14,15] Perhaps not surprisingly, renal failure is thus more common as a presentation in IgD MM, with an incidence reported to be as high as 36%.[16] There is also therefore a very high frequency of Bence Jones proteinuria in more than 90% of patients with IgD MM.[9,14] Interestingly, in a large series of more than 1,200 myeloma patients in whom gene expression profiling was pursued, 1% were identified as having IgD MM, and high-risk myeloma was found in 38% of these IgD MM patients in the higher-risk proliferation subgroup.[17] These patients had a higher percentage of adverse cytogenetic abnormalities, as well as higher levels of lactate dehydrogenase, beta-2 microglobulin, and C-reactive protein, findings consistent with poor prognosis and shorter overall survival (OS) time.[17]

Given the generally worse prognosis with IgD MM, what are the therapeutic implications? Clues to promising newer treatment approaches are provided by comparisons between the 2010 study by Morris and colleagues,[15] which examined efficacy and outcome of autologous transplantation in rare myelomas, and studies by other investigators in earlier series.[9] Specifically, median OS of patients with IgD MM treated with novel agents and autologous stem cell transplant (ASCT) improved to approximately 43 months in the study by Morris et al,[15] compared with a median OS of 21 months reported in 1994 by Bladé et al.[9] Drs. Pandey and Kyle conclude that with novel agent therapy (including thalidomide, bortezomib, and lenalidomide) that is specifically integrated with ASCT when feasible, survival for IgD MM is improving; however, they note that outcomes remain inferior to those achieved in patients with other myeloma isotypes, highlighting the need for better and more innovative approaches in treatment.

Insights into IgE MM are limited by its rarity and by the fact that it accounts for only 0.01% of all patients with myeloma. Macro and colleagues reported a median age of 62 years at diagnosis, as well as a preponderance to affect men over women. Clinical features are otherwise very similar to those of IgD MM as detailed above, although with the important distinction of an increased incidence of PCL.[4] While evaluation and management of IgE MM are similar to the approach used for other

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isotypes, disease monitoring in IgE MM may be difficult due to excess antigen.[18] Interestingly, a recent report describes an increase in serum Krebs von den Lungen–6 (KL-6) levels in IgE MM, suggesting that the monitoring of KL-6 levels could be used for disease evaluation.[19] As seen for IgD MM, the median OS in IgE MM tends to be shorter than that of other isotypes; in this regard, a particularly important series highlighted by the Pandey and Kyle review is again that of Morris et al,[15] in which the OS in the 13 IgE MM patients was just 33 months, compared with 62 months for patients with the other, more common myeloma subtypes.

While IgD MM and IgE MM are uncommon variants of myeloma, currently available targeted agents and new drugs now in development have the potential to substantially improve outcome. The treatment series reviewed by Drs. Pandey and Kyle demonstrate convincingly that combination approaches with novel agents followed by ASCT for eligible patients constitute an appropriate therapeutic strategy. This is becoming increasingly apparent in the treatment of myeloma; more broadly, combination strategies are critical in targeting both myeloma and the bone marrow microenvironment, thereby overcoming powerful anti-apoptotic mechanisms that otherwise drive tumor cell survival.[20] Specifically, an emerging standard of care in myeloma, both in the relapsed/refractory setting and in patients with earlier disease, is the use of proteasome inhibitors together with immunomodulators and steroids as part of a therapeutic backbone that includes additional agents.[21] Broadly, the impact of these combinatorial strategies has had a major positive effect on prognosis, and in particular the inclusion of proteasome inhibitors and immunomodulatory agents as part of initial treatment has improved the outcome in ASCT, as well as in other settings.[21] Given the tendency of both IgD MM and IgE MM toward extramedullary spread, development of PCL, and associated renal involvement, the real promise of improving patient outcome in these rare but important myeloma variants lies in utilization of multi-drug combinations to overcome resistance, use of next-generation agents and monoclonal antibodies to counter adverse biology, and integration of immunotherapy to combat minimal residual disease.[22] As Drs. Pandey and Kyle presciently conclude, these strategies do, indeed, warrant inclusion in current and future translational clinical studies.

Acknowledgements: *The authors gratefully acknowledge the administrative support of Michelle Maglio in the preparation of this commentary.*

Financial Disclosure: *Dr. Richardson has served on advisory committees for Millennium, Celgene, Novartis, Johnson & Johnson, Genmab, and Bristol-Myers Squibb. Dr. Anderson serves on the advisory committees of Celgene, Onyx, Bristol-Myers Squibb, Johnson & Johnson, Sanofi-Aventis, and Gilead. He is a scientific founder of, and owns stock in, Acetylon Pharmaceuticals and OncoPep. The remaining authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.*

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