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Unusual Myelomas: A Review of IgD and IgE Variants

Abstract: Immunoglobulin D multiple myeloma (IgD MM) accounts for almost 2% of all myeloma cases. It is associated with an increased frequency of undetectable or small monoclonal (M)-protein levels on electrophoresis; osteolytic lesions; extramedullary involvement; amyloidosis; a lambda (λ) light chain predilection; renal failure; hypercalcemia; and, often, advanced disease at diagnosis. Immunoglobulin E (IgE) MM is rare, with fewer than 50 cases reported in the literature. IgE MM presents with features similar to those of IgD MM, along with a higher incidence of plasma cell leukemia. The hallmark of IgE MM is t(11;14)(q13;q32). IgD and IgE levels are generally very low and hence may escape detection; thus, it is important that, when myeloma is suspected, patients be screened for the presence of IgD and IgE if they have an apparently free monoclonal immunoglobulin light chain in the serum. Although survival of patients with IgD MM or IgE MM is shorter in comparison to those with immunoglobulin G (IgG) MM or immunoglobulin A (IgA) MM, the outcome for patients with IgD and IgE subtypes is improving with the use of novel agents and autologous transplantation.

Introduction

Multiple myeloma (MM) is a neoplastic condition whose hallmark is the proliferation of malignant plasma cells in the bone marrow, resulting in an increase in serum and/or urine monoclonal (M) protein and end-organ damage, including hypercalcemia, renal failure, anemia and/or bone lesions, commonly described by the acronym CRAB.[1] The interaction of stromal and plasma cells produces immunoglobulins (Igs), which are proteins synthesized by immunocompetent cells.[1] These immunoglobulins form the body's humoral defense against infections and allergens. There are five kinds of immunoglobulins and two types of polypeptides, known as the heavy and light chains. The structurally specific heavy chains in each class of Ig are referred to as gamma (G), alpha (A), mu (M), delta (D), and epsilon (E). The two light chains, kappa (κ) and lambda (λ), are immunologically distinct and common to all immunoglobulins. These immunoglobulins have a protective function in the human immune system, and a pathologic derangement leading to an increase in one type of immunoglobulin, resulting in a monoclonal gammopathy. In multiple myeloma, IgG, IgA, and light chains predominate, with a prevalence of 52%, 21%, and 16%, respectively, comprising almost 90% of all myeloma types. The remainder consists of IgD, IgE, IgM, and nonsecretory types.[2] In this review, we will focus our discussion on IgD and IgE variants of myeloma.

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IgD Myeloma

IgD secreting plasma cells originate from germinal center B cells due to somatic hypermutation of IgV re-

gions,[3] while t(11;14)(q13;q32) translocation has been reported as a characteristic feature of IgE MM.[4] IgG and IgA have a serum concentration of 1,020 mg/dL to 1,460 mg/dL and 210 mg/dL to 350 mg/dL, respectively; the level of IgD in serum is 0 to 10 mg/dL, whereas IgE may be present only in trace amounts. Thus, in IgD MM and IgE MM, there may only be a small or unrecognizable M-protein spike on electrophoresis. This may lead to diagnostic errors in identifying these patient subgroups.

Epidemiology, incidence, and presentation

After IgD MM was first reported by Rowe and Fahey[5] in 1965, multiple studies have reported an IgD MM prevalence of approximately 1% to 2% of myeloma patients,[2,6-9] whereas IgE is rare, with fewer than 50 cases reported in the literature.[10] Another study found an IgD MM incidence of 6% in myeloma patients younger than 40 years.[11] Given their rarity, knowledge about these diseases is gained mostly from a few single-center case series and isolated case reports. Although the clinical features of IgD MM are similar to those of IgG MM, IgA MM, and light chain myeloma, IgD MM has been recognized as involving relatively younger patients, with a median age of 52 to 60 years at onset; occurring predominantly in males; and being characterized by a small or absent M-protein spike on electrophoresis, as previously noted, as well as extramedullary involvement, osteolytic lesions, presence of systemic amyloidosis, hypercalcemia, a λ light chain bias, Bence Jones proteinuria (BJP), renal failure, and a shorter survival time[6-9] (Table 1). Another feature of

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IgD MM is the presence of advanced disease at the time of diagnosis. Shimamoto et al reviewed 165 Japanese patients with IgD MM classified according to the Durie-Salmon (DS) staging system.[12] They found 7% of patients to be DS stage I, 22% DS stage II, and 71% DS stage III. Similarly, a staging of 379 IgD patients in another study[8] reported 6%, 17%, and 77% in DS stages I, II, and III, respectively. However, two studies found no significant relationship between DS stage and survival outcomes in patients with IgD MM.[12,13] Because of the limited number of patients, an attempt to create a prognostic system for IgD MM has not been successful. Jancelewicz et al[7] reported that hemoglobin and serum albumin were important prognostic features; however, the methods for this analysis were not described, and only a limited number of parameters were analyzed. Similarly, Shimamoto et al[12] proposed that light chain subtype and white blood cell count (WBC) were significant predictors of survival. In their study, patients were divided into four groups depending on the type of light chain (κ or λ) and WBC count above or below $7 \times 10^9/L$. The group with the κ subtype and WBC counts $< 7 \times 10^9/L$ was considered to be at low risk, with a 5-year overall survival (OS) of 66%, while OS in the intermediate group was 22.5% and in the high-risk group was 0%. In a series of 1,202 myeloma patients, including 12 (1%) with IgD MM, gene-expression profiles (GEPs) defining high-risk MM were found in all Ig isotypes. A total of 38% of the IgD myeloma patients, in comparison with 10% of the overall cohort, were included in the proliferation subgroup ($P = .003$). Other factors associated with IgD were more common occurrence of cytogenetic abnormalities, elevated serum lactate dehydrogenase (LDH), beta-2 microglobulin (B2M), and C-reactive protein (CRP) values; these features could account for an increased proliferation subtype, which

might help to explain the shorter OS in IgD myeloma.[14]

With advanced disease, myeloma cells tend to become independent of the bone marrow microenvironment. This is at least partially responsible for the spread of plasma cells to the peripheral blood, thereby manifesting as plasma cell leukemia (PCL; defined as peripheral blood plasma cells $> 2 \times 10^9/L$ and/or $> 20\%$ plasma cells in the peripheral blood) or soft-tissue plasmacytomas.[15] IgD MM has been reported to have a more aggressive course and a poor prognosis, with patients having a median survival of less than 2 years prior to the availability of novel agents and use of autologous transplantation.[6] Interestingly, response to therapy both before and after autologous stem cell transplantation (ASCT) has been reported to be better in patients with IgD MM compared with other isotypes; however, this does not translate into increased survival.[8] Morris et al reported complete response (CR) rates of 12% vs 20% after conditioning, and 28% vs 44% following transplantation in non-IgD vs IgD MM, respectively. The progression-free survival (PFS) was reported as 27 months vs 24 months ($P = .017$), while median OS was 62 months vs 43 months ($P = .0001$) in non-IgD vs IgD MM, respectively.[8] This significant improvement in survival (eg, compared with the median OS of 21 months reported by Bladé et al[6]) is due to treatment with novel agents (thalidomide, bortezomib, lenalidomide) and ASCT. With use of novel agent therapy and ASCT, survival is improving, although it is still inferior to survival of IgG, IgA, and light chain MM.[6-9,13,16]

The most common presenting symptoms in IgD myeloma are similar to those of IgG and IgA myeloma, and include bone pain, weakness, fatigue, and weight loss.[6] A higher frequency of skeletal involvement occurs in IgD MM, with more than 72% of patients reporting bone pain.[6,7] While one study re-

Table 1 Salient Features of IgD Multiple Myeloma

Median age: 52 to 60 years
Male gender
Advanced disease at diagnosis (Durie-Salmon stage 3)
Small or absent M-spike
Extramedullary involvement
Osteolytic lesions
Amyloidosis
Anemia
Hypercalcemia
Lambda light chain expression
Bence Jones proteinuria
Renal failure
Poor prognosis

IgD = immunoglobulin D.

ported the incidence of osteolytic lesions as 42%, [12] Bladé et al[6] found that 77% had an abnormal skeletal survey.

While the incidences of hepatomegaly, splenomegaly, and lymphadenopathy were reported as 55% each by Jancelewicz et al,[7] organomegaly was reported to occur in 13%, 6%, and 9% of patients, respectively, in another study.[6] Shimamoto et al reported a 26% incidence of hepatomegaly, 12% splenomegaly, and 10% lymphadenopathy in IgD MM.[12] Bladé et al[6] found no significant difference in the recognition of hepatomegaly and splenomegaly in comparison with IgG, IgA, and light chain MM, but lymphadenopathy was more common in IgD than in other isotypes. Symptoms attributable to amyloidosis, such as carpal tunnel syndrome and macroglossia, were reported in 19%.[6] Other symptoms included higher rates of extramedullary plasmacytoma (EMP), which sometimes presented as an extradural tumor[6] or nerve root compression.[17]

Amyloidosis has been reported to commonly affect patients with IgD

MM. As noted, Bladé et al[6] found amyloidosis in 19% of patients. In an autopsy series, 10 of 23 patients (44%) had amyloidosis.[7] In another series of 53 patients with IgD and amyloidosis, fatigue; peripheral edema; carpal tunnel syndrome; macroglossia; cardiac, renal, or hepatic involvement; and peripheral neuropathy were reported as presenting complaints.[18] These 53 cases of IgD-related amyloidosis were compared with 144 cases of non-IgD monoclonal protein-related amyloidosis. Cardiac amyloidosis was found in 45% vs 56% of patients with IgD vs non-IgD amyloidosis ($P = .047$), and renal amyloidosis was noted in 36% vs 58% of these two groups of patients ($P = .005$). Survival outcomes in patients with IgD amyloidosis were not different from those of patients with IgG, IgA, or light chain myeloma amyloidosis.[18] In another study, t(11;14) was associated with poorer outcomes in light chain amyloidosis. There was a significant survival disadvantage (hazard ratio [HR] = 2.1; 95% confidence interval [CI], 1.04–6.39; $P = .04$) for patients with the t(11;14) translocation.[19]

EMP may be palpable or observed radiographically as masses around bones or in soft tissue. EMP is reported to occur in 13% to 19% of myeloma patients[2,6,20]; however, a 19% to 63% prevalence of EMP associated with IgD MM in particular has been reported.[6,12,16] Usmani et al evaluated extramedullary disease (EMD) in 1,965 patients in whom a baseline positron emission tomography (PET)-CT and subsequent PET-CT at relapse were available. Patients were grouped as EMD-1 (EMD at diagnosis) or EMD-2 (EMD at subsequent relapse). EMD-1 was found in 3.3% of patients (66 of 1,965) with the most common sites of involvement in the chest wall, liver, lymph nodes, skin, soft tissue, and paraspinal areas. The incidence of EMD-2 was reported in 1.8% of patients at relapse or disease progression,

with the liver as the most common site of involvement. The OS was 31% at 5 years ($P < .001$) in EMD-1 compared with 59% in those without EMD. The PFS was 21% vs 50% at 5 years ($P < .001$) in patients with EMD-1 compared with those without EMD. A combined cumulative incidence of EMD (both 1 and 2) 5 years post-transplant was higher in those with GEP-defined high-risk features (11% vs 2%; $P < .001$), pre-transplant cytogenetic abnormalities (7% vs 4%; $P = .004$), anemia (9% vs 3%, $P < .001$), and thrombocytopenia (9% vs 3%; $P < .001$).[21]

A study looking at the outcome of EMD reported a significantly shortened PFS (18 months vs 30 months; $P = .003$) but no statistically significant difference in OS (36 months vs 43 months; $P = .36$) in those who had EMD at diagnosis compared with those who did not.[20] Hobbs and Corbett[16] suggested that EMPs be classified as (1) those breaking the cortex of the bone and growing locally or (2) those developing within soft tissue. They also noted that EMP was more common in those with increased BJP (93%) and λ light chain expression (90%). Bladé et al[6] reported that 10 of 53 patients (19%) with IgD myeloma had EMP. Extradural tumors were found in 7 of the 10 patients. Eight additional patients developed an EMP later in the course of disease. There have also been reports of spinal and nerve root compressions resulting in neurological deficits.[17] Patients with IgD MM presenting as a testicular tumor who subsequently developed abdominal masses and ascites have been described.[22] Chromosomal analysis of cells obtained from the ascitic fluid revealed aneuploidy and complex abnormalities, including 1q+, 2p+, and 14q+.

PCL is a rare extramedullary manifestation of myeloma and has a poor clinical outcome. As previously noted, it is defined by the presence of $> 2 \times 10^9$ /L circulating plasma cells and/or circulating plasma cells $> 20\%$.[23,24] PCL is present in 2% to 5% of patients

with IgD myeloma and can present de novo (primary PCL) or as secondary disease that develops in patients with advanced myeloma. Prognosis is very poor in secondary PCL. Noel and Kyle reported that patients with secondary PCL were usually elderly, with a higher incidence of lytic lesions and thrombocytopenia and a median survival of only 1.3 months.[24] Some reports suggest that PCL is associated with IgD myeloma,[24,25] while others show an association with IgE.[26] A higher incidence of t(11;14)(q13;q32) was reported to be associated with PCL,[27] while another study reported t(11;14) as the hallmark feature of IgE myeloma.[4]

Pertinent laboratory values reported in IgD myeloma include a higher frequency of anemia (Hb < 10 g/dL) [6,9,13]; hypercalcemia (> 11 mg/dL in 22% to 30%)[6,7]; elevated creatinine levels (> 2 mg/dL in 33% to 54%) [6,12]; a bias for λ light chain over κ [6-9,12]; the common occurrence of cytogenetic abnormalities; and, as previously mentioned, elevated levels of serum LDH, B2M, and CRP.[14] While platelet counts were usually within normal limits, occurrence of thrombocytosis was associated with amyloidosis in one study.[6] A serum M-spike of > 2 g/dL was noted in only 14% of IgD MM patients, while a urine light chain M component on electrophoresis of > 4 g/day was observed in 28% of patients.[6] The same study also reported a urinary M-protein level of > 1 g/d in more than 60% of patients. [6] Urinary light chain at diagnosis was reported in 61% of patients by Reece et al.[9] A lower M-protein level, and higher serum albumin and B2M levels, were reported in another study.[8]

The bias for λ light chain expression with a reversed light chain ratio is a characteristic feature of IgD MM.[6-8]

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8,12,13] Bladé et al reported λ light chain expression in 60% of patients with IgD MM,[6] Shimamoto et al reported it in 82%,[12] Jancelewicz et al reported it in 90%,[7] and Morris et al reported λ light chains in 75% of patients.[8] Median survival of patients with κ vs λ light chains was 20 months and 29 months, respectively ($P = .99$). [6] Renal failure is more common at presentation in IgD MM. An increase in serum creatinine (> 2 mg/dL) has been reported in various series of IgD MM.[6,7,12] Bladé et al found an elevated creatinine level (> 2 mg/dL) in 33% of patients with IgD MM,[6] and Reece et al reported elevated creatinine in 36% of patients with this variant.[9] BJP was noted in more than 90% of IgD MM patients.[6,7] The combination of increased creatinine levels, hypercalcemia, hyperuricemia, and light chain excretion is often associated with renal insufficiency in IgD MM.[28] In performing quantitative measurements of individual immunoglobulins, Shimamoto et al[12] saw a decrease in serum levels of IgG (in 52% of patients), of IgA (in 53%), and of IgM (in 46%), along with an increase in IgD (> 12 g/dL). Similar results were reported by Bladé et al,[6] in that 84% of IgD MM patients had a reduction in one or more uninvolved immunoglobulin levels on quantitative measurements.

Evaluation and management

The evaluation of a patient suspected of having IgD MM begins with a complete history and physical examination. All multiple myeloma patients with an apparently free light chain without an IgG or IgA M-protein must be screened for the presence of IgD and IgE. As mentioned previously, the amount of IgD and IgE immunoglobulin in the serum may be very low and can escape detection with electrophoresis. Patients are sometimes given a false diagnosis of nonsecretory or light chain myeloma, but as mentioned earlier, IgD myeloma is often overlooked initially.

The management of IgD MM is not

different from that of IgG MM, IgA MM, or light chain MM, and encompasses novel chemotherapy regimens and ASCT.

Bladé et al[6] reported a median OS of 21 months, with 3-year and 5-year survivals of 36% and 21%, respectively. The same study also found a trend toward better survival in patients treated with combination chemotherapy compared with those given single alkylating agents (median, 64 vs 20 months; $P = .09$). Median survival in Japanese patients with IgD MM was reported as 12 months in one study,[12] while another investigation reported OS at 13.7 months.[7]

Recent studies comparing outcomes following chemotherapy alone vs ASCT show a significant benefit in survival when patients are treated with high-dose therapy followed by ASCT.[8,9,29,30] In a study of 26 patients with IgD MM, 39% received chemotherapy followed by ASCT, while 50% were given only chemotherapy. The median PFS was 18 months for those receiving both chemotherapy and ASCT vs 20 months for patients treated with chemotherapy alone, while the median OS was not reached for the ASCT group and was 16 months for those who received only conventional chemotherapy.[29] Wechalekar et al[30] also compared outcomes of IgD patients following ASCT vs chemotherapy. The median PFS after ASCT was not reached after a median follow-up of 4 years; in comparison, median PFS was 1.2 years in the chemotherapy group. The mean OS following ASCT was 5.1 years vs 2 years for chemotherapy alone ($P = .09$). Sharma et al reported that 15 of 17 IgD MM patients underwent ASCT. The 3-year PFS and OS rates in these 15 patients were 38% and 64%, respectively. The median PFS was 18 months, whereas the median OS was 45 months. A comparison of these outcomes with results in 104 patients with non-IgD MM who underwent ASCT showed no significant difference in PFS or OS ($P = .86$ and $P = .74$, respectively).[31] Morris et al reported

20% CR and 66% partial responses (PR) following induction chemotherapy, and 44% CR and 66% CR/PR following transplantation.[8] The median PFS was 23.7 months and the median OS was 43.5 months in patients with IgD MM, compared with an OS of 63.5 months in those with IgG, IgA, or light chain MM. Although reported survival in IgD MM was less than that of patients with IgG MM, IgA MM, and light chain MM, it was still better than survival outcomes in non-transplanted IgD patients.[8,9]

In a similar study, Reece et al reported comparable outcomes in all myeloma isotypes and recommended that ASCT be offered to all eligible patients.[9] The median follow-up was 41 months (range, 2–130 months) for IgD MM, whereas the median time from diagnosis to transplantation was 9 months. The PFS was 79% at 1 year and 38% at 3 years, while the OS was 87% at 1 year and 69% at 3 years in IgD MM. The PFS for patients with IgG MM was 78% at 1 year and 49% at 3 years. The OS at 1 year and 3 years was 86% and 63%, respectively.

However, a Korean study of patients who underwent ASCT after high-dose chemotherapy reported median event-free survival (EFS) and OS of 6.9 months and 12 months in patients with IgD MM, compared with EFS and OS of 11.5 months and 55.5 months, respectively, in patients with IgG MM, IgA MM, and light chain MM.[32] A summary of selected myeloma studies both before and during the era of novel agents and transplantation is presented in Table 2. Although cure is rare in myeloma, one patient with IgD MM was considered to have been cured and was disease-free after 21 years of treatment. He died of an unrelated bronchogenic carcinoma, and a post-mortem exam confirmed the absence of myeloma.[33]

IgE Myeloma

IgE MM is a rare disease, accounting for only 0.01% of all patients with MM.[34] The first case was reported in 1967,[35]

and fewer than 50 cases have been described to date.[10] In one reported case, a patient with IgE monoclonal gammopathy of undetermined significance was followed for 12 years before developing symptomatic MM.[36] Given the rarity of IgE MM, knowledge about this condition is gathered from isolated case reports and a few small case series. A review of 29 published cases by Macro et al reported a mean age at diagnosis of 62 years, with a slight preponderance of male patients. The clinical features of IgE MM are similar to those of IgG MM, IgA MM, and light chain MM, as well as IgD MM.[37] Bone pain, anemia, renal failure, hypercalcemia, BJP, amyloidosis, and an increased incidence of PCL are frequently noted. The median survival of the 29 patients reported by Macro et al was 16 months. The presence of t(11;14)(q13;q32) was reported in 83% of patients with IgM MM, IgE MM, and non-secretory MM. This was five-fold greater than the rate reported in patients with IgD MM. Thus, this translocation is a hallmark of IgE MM.[4] Although survival time is generally short, a patient diagnosed with IgE MM at the age of 56 survived for more than 20 years and died of chronic comorbidities at age 77.[38]

The process of evaluation and management of IgE MM is similar to that of the other isotypes.[39] Monitoring of disease response in IgE MM may be difficult, because of excess antigen levels.[26] Hua et al reported an increase in serum Krebs von den Lungen-6 (KL-6) levels in IgE MM and suggested that KL-6 be used for disease monitoring.[10]

Morris et al, reporting on a series of 13 patients with IgE MM, noted CR rates of 60% following ASCT, compared with 28% CR overall for patients with IgG MM, IgA MM, and light chain MM.[8] The median PFS was the same in both groups. The median OS was 33 months in the 13 patients with IgE MM, compared with a median OS of 62 months for the common myeloma types.

In conclusion, IgD MM and IgE

Table 2 IgD Multiple Myeloma Treatment Outcomes in Different Series

Reference	PFS (mos)	OS (mos)
Bladé et al[6] (N = 53)	NR	21.4
Jancelewicz et al[7] (N = 133)	NR	13.7
Morris et al[8] (N = 379)	23.7	43.5
Reece et al[9] (N = 36)	At 1 yr: 79% At 3 yrs: 38%	At 1 yr: 87% At 3 yrs: 69%
Shimamoto et al[12] (N = 165)	NR	12
Fibbe and Jansen[13] (N = 21)	NR	17

IgD = immunoglobulin D; NR = not reported; OS = overall survival; PFS = progression-free survival.

MM are uncommon variants of myeloma. Their clinical features are similar to those of the other isotypes, but there appears to be an increased incidence of amyloidosis and EMD in IgD MM, and an increased incidence of PCL in IgE MM. When there is a suspicion of the diagnosis of myeloma and only monoclonal light chain is detected in the serum or urine, the patient must be screened for the presence of IgD and IgE monoclonal protein. Although the response to chemotherapy and ASCT is satisfactory, the OS has been shorter. However, most of the reported data on IgD MM and IgE MM were reported before availability of the novel agents that are now used in this setting (thalidomide, bortezomib, and lenalidomide). The response to treatment in patients with IgD MM is similar to that of patients with other myeloma isotypes; however, survival time is generally shorter than in patients with the common myelomas. In the current era of novel therapy and autologous transplantation, reported survival was improved for patients with IgD MM who underwent ASCT, compared with those who did not. More studies are needed to help us better understand the biology of rare myelomas and to further improve outcomes for patients.

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REFERENCES

1. Kyle RA, Rajkumar SV. Multiple myeloma. *N Engl J Med*. 2004;351:1860-73.
2. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic Proc*. 2003;78:21-33.
3. Arpin C, de Bouteiller O, Razanajao D, et al. The normal counterpart of IgD myeloma cells in germinal center displays extensively mutated IgVH gene, Cmu-Delta switch, and lambda light chain expression. *J Exp Med*. 1998;187:1169-78.
4. Avet-Loiseau H, Garand R, Lode L, et al. Translocation t(11;14)(q13;q32) is the hallmark of IgM, IgE, and non-secretory multiple myeloma variants. *Blood*. 2003;101:1570-1.
5. Rowe DS, Fahey JL. A new class of human immunoglobulins. I. A unique myeloma protein. *J Exp Med*. 1965;121:171-84.
6. Bladé J, Lust JA, Kyle RA. Immunoglobulin D multiple myeloma: presenting features, response to therapy, and survival in a series of 53 cases. *J Clin Oncol*. 1994;12:2398-404.
7. Jancelewicz Z, Takatsuki K, Sugai S, Pruzanski W. IgD multiple myeloma. Review of 133 cases. *Arch Intern Med*. 1975;135:87-93.
8. Morris C, Drake M, Apperley J, et al. Efficacy and outcome of autologous transplantation in rare myelomas. *Haematologica*. 2010;95:2126-33.
9. Reece DE, Vesole DH, Shrestha S, et al. Outcome of patients with IgD and IgM multiple myeloma undergoing autologous hematopoietic stem cell transplantation: a retrospective CIBMTR study. *Clin Lymphoma Myeloma Leuk*. 2010;10:458-63.
10. Hua J, Hagihara M, Inoue M, Iwaki Y. A case of IgE-multiple myeloma presenting with a high serum Krebs von den Lungen-6 level. *Leuk Res*. 2012;36:e107-9.
11. Bladé J, Kyle RA, Greipp PR. Presenting features and prognosis in 72 patients with multiple myeloma who

were younger than 40 years. *Brit J Haematol*. 1996;93:345-51.

12. Shimamoto Y, Anami Y, Yamaguchi M. A new risk grouping for IgD myeloma based on analysis of 165 Japanese patients. *Eur J Haematol*. 1991;47:262-7.

13. Fibbe WE, Jansen J. Prognostic factors in IgD myeloma: a study of 21 cases. *Scand J Haematol*. 1984;33:471-5.

14. Nair B, Waheed S, Szymonifka J, et al. Immunoglobulin isotypes in multiple myeloma: laboratory correlates and prognostic implications in total therapy protocols. *Brit J Haematol*. 2009;145:134-7.

15. Mitsiades CS, McMillin DW, Klippel S, et al. The role of the bone marrow microenvironment in the pathophysiology of myeloma and its significance in the development of more effective therapies. *Hematol Oncol Clin North Am*. 2007;21:1007-34, vii-viii.

16. Hobbs JR, Corbett AA. Younger age of presentation and extraosseous tumour in IgD myelomatosis. *Br Med J*. 1969;1:412-4.

17. Lolin YI, Lam CW, Lo WH, et al. IgD multiple myeloma with thoracic spine compression due to epidural extraosseous tumour spread. *J Clin Pathol*. 1994;47:669-71.

18. Gertz MA, Buadi FK, Hayman SR, et al. Immunoglobulin D amyloidosis: a distinct entity. *Blood*. 2012;119:44-8.

19. Bryce AH, Ketterling RP, Gertz MA, et al. Translocation t(11;14) and survival of patients with light chain (AL) amyloidosis. *Haematologica*. 2009;94:380-6.

20. Varettoni M, Corso A, Pica G, et al. Incidence, presenting features and outcome of extramedullary disease in multiple myeloma: a longitudinal study on 1003 consecutive patients. *Ann Oncol*. 2010;21:325-30.

21. Usmani SZ, Heuck C, Mitchell A, et al. Extramedullary disease portends poor prognosis in multiple myeloma and is over-represented in high-risk disease even in the era of novel agents. *Haematologica*. 2012;97:1761-7.

22. Ishii K, Yamato K, Kubonishi I, et al. IgD myeloma presenting as a testicular tumor: establishment and characterization of an IgD-secreting myeloma cell line. *Am J Hematol*. 1992;41:218-24.

23. Kyle RA, Maldonado JE, Bayrd ED. Plasma cell leukemia. Report on 17 cases. *Arch Intern Med*. 1974;133:813-8.

24. Noel P, Kyle RA. Plasma cell leukemia: an evaluation of response to therapy. *Am J Med*. 1987;83:1062-8.

25. Garcia-Sanz R, Orfao A, Gonzalez M, et al. Primary plasma cell leukemia: clinical, immunophenotypic, DNA ploidy, and cytogenetic characteristics. *Blood*. 1999;93:1032-7.

26. Talamo G, Castellani W, Dolloff NG. Prozone effect of serum IgE levels in a case of plasma cell leukemia. *J Hematol Oncol*. 2010;3:32.

27. Avet-Loiseau H, Daviet A, Brigaudeau C, et al. Cytogenetic, interphase, and multicolor fluorescence in situ hybridization analyses in primary plasma cell leukemia: a study of 40 patients at diagnosis, on behalf of the Intergroupe Francophone du Myelome and the Groupe Francais de Cytogetique Hematologique. *Blood*. 2001;97:822-5.

28. Kyle RA. Multiple myeloma: review of 869 cases. *Mayo Clinic proceedings*. Mayo Clinic. 1975;50:29-40.

29. Maisnar V, Hajek R, Scudla V, et al. High-dose chemotherapy followed by autologous stem cell transplantation changes prognosis of IgD multiple myeloma. *Bone Marrow Transplant*. 2008;41:51-4.

30. Wechalekar A, Amato D, Chen C, et al. IgD multiple

myeloma—a clinical profile and outcome with chemotherapy and autologous stem cell transplantation. *Ann Hematol*. 2005;84:115-7.

31. Sharma M, Qureshi SR, Champlin RE, et al. The outcome of IgD myeloma after autologous hematopoietic stem cell transplantation is similar to other Ig subtypes. *Am J Hematol*. 2010;85:502-4.

32. Chong YP, Kim S, Ko OB, et al. Poor outcomes for IgD multiple myeloma patients following high-dose melphalan and autologous stem cell transplantation: a single center experience. *J Korean Med Sci*. 2008;23:819-24.

33. Kyle RA. IgD multiple myeloma: a cure at 21 years. *Am J Hematol*. 1988;29:41-3.

34. Jako JM, Gesztes T, Kaszas I. IgE lambda monoclonal gammopathy and amyloidosis. *Int Arch Allergy Immunol*. 1997;112:415-21.

35. Johansson SG, Bennich H. Immunological studies of an atypical (myeloma) immunoglobulin. *Immunology*. 1967;13:381-94.

36. Ludwig H, Vormittag W. "Benign" monoclonal IgE gammopathy. *Br Med J*. 1980;281:539-40.

37. Macro M, André I, Comby E, et al. IgE multiple myeloma. *Leuk Lymphoma*. 1999;32:597-603.

38. Hayes MJ, Carey JL, Krauss JC, et al. Low IgE monoclonal gammopathy level in serum highlights 20-yr survival in a case of IgE multiple myeloma. *Eur J Haematol*. 2007;78:353-7.

39. Dimopoulos M, Kyle R, Fermand JP, et al. Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. *Blood*. 2011;117:4701-5.

THE PANDEY/KYLE ARTICLE REVIEWED: PAUL G. RICHARDSON ET AL

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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