Extramedullary relapse of multiple myeloma associated with a shift in secretion from intact immunoglobulin to light chains

Biological therapies in multiple myeloma have heralded a new and exciting era for treatment to combat this disease. However the evolutionary pressures that these drugs place on the microenvironment has resulted in a change in the biological behaviour of this malignancy and novel manifestations of relapsed disease. This is illustrated in our series of three patients showing fulminant relapse of disease with plasmablastic features, an extramedullary predilection and a shift in secretion from intact immunoglobulin to free light chains only.

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Multiple myeloma is a clonal malignancy of plasma cells characterized in part by the development of a serum monoclonal protein. The immunoglobulin produced by the neoplastic plasma cells can be of any immunoglobulin class and in more than 80% of patients is present as an intact immunoglobulin (IIG) composed of heavy and light chains.[1] Of those patients with intact immunoglobulin multiple myeloma (IIGMM), 95% also have abnormal serum free light chain (SFLC) concentrations.[2] As the vast majority of patients with IIGMM show parallel fluctuations of their IIG and SFLC, the utility of SFLC assays in these patients has been questioned.[3] The era of stem cell transplantation and biological therapies including thalidomide and its analogs has changed the natural history of myeloma. This selective pressure has culminated in novel manifestations of relapsed disease. This is evidenced by our presentation of three patients with florid extramedullary relapse with a marked increase in SFLC in the absence of a parallel rise in IIG – light chain escape from plateau phase (LEPP)

All three patients were diagnosed with IIGMM in which there was initially a parallel correlation of the IIG level with disease activity. Serial measurements of SFLC were not performed throughout their disease however, urinary Bence-Jones protein (UBJP) levels were assayed with each measurement of IIG and failed to show any discrepancy until the onset of LEPP. The onset of LEPP in these patients was heralded by a fulminant relapse of their disease associated with a marked rise in their SFLC but no alteration in their IIG levels (Figure 1). Common features accompanying the presentation of LEPP included multiple extramedullary sites of relapse, plasmablastic morphology, acute renal failure, a raised lactate dehydrogenase and β_2-microglobulin. An important feature preceding the onset of LEPP was the use of biological therapies, in particular thalidomide and lenalinomide. LEPP followed an aggressive clinical course, with the subsequent therapies employed offering only marginal benefits.

Case 1: A 63-year old man diagnosed with IgA-κ IIGMM with no detectable UBJP achieved a good partial response to induction therapy. He refused autologous stem-cell transplantation and was commenced on thalidomide when his disease progressed. He achieved a complete response (CR) on thalidomide and was maintained on this for 11 months. He ceased thalidomide due to intolerable somnolence and constipation. Five months later he had a florid relapse of his disease with features of LEPP (Figure 1).

Case 2: A 68-year old woman diagnosed with IgG-λ IIGMM with no detectable UBJP had a protracted course

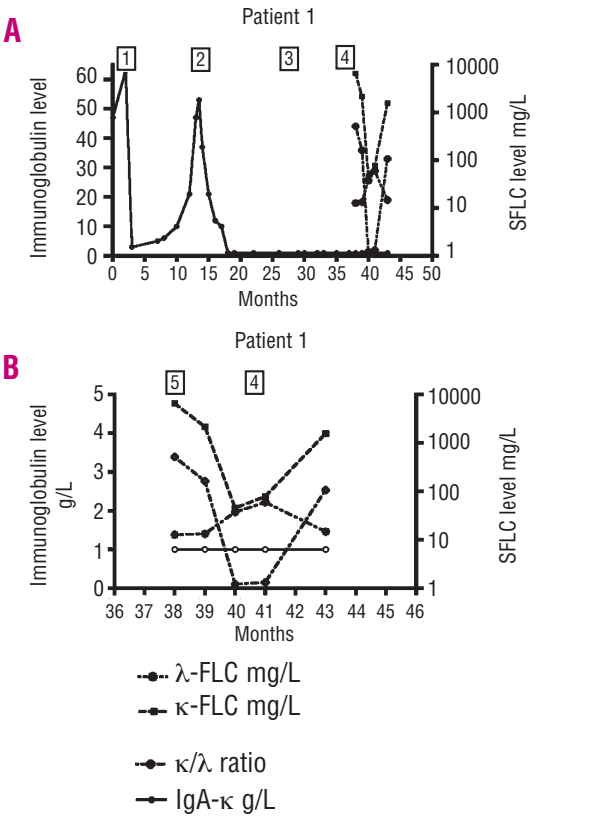

Figure 1. 1A. A temporal sequence illustrating the dramatic development of LEPP. **1B.** A more detailed view of the changes in immunoglobulin levels following the onset of LEPP. 1) Induction with 4 cycles of cyclophosphamide, idarubicin and dexamethasone, 2) thalidomide commenced as a result of progressive disease, 3) thalidomide ceased due to side-effects, 4) fulminant relapse of disease with onset of LEPP, 5) intermediate dose melphalan (25mg/m^2) given as salvage therapy, 5) melphalan and prednisolone given as further salvage with little effect. It should be noted that light chains were not detected by protein electrophoresis and immunofixation electrophoresis on urine at diagnosis or throughout the course of the illness until the development of LEPP. Serum free light chains were detected using previously described methods.[12]

with multiple therapies employed to control her disease. As a consequence of progressive disease she commenced thalidomide and achieved a near CR. She was maintained on this therapy until a dramatic extramedullary relapse with the features of LEPP.

Case 3: A 69-year old woman initially diagnosed with IgA-κ IIGMM had a CR to a course of dexamethasone and commenced lenalinomide as part of a clinical trial. Two months following this she had relapsed in multiple extramedullary sites and demonstrated features of LEPP.

More detailed clinical information about the patients is summarized in Table 1.

The ability of plasma cells to produce IgG or IgA instead of IgM requires a complex rearrangement of the IgH gene. This switching process usually occurs on one allele whilst in a large proportion of MM the other allele is involved in translocations with putative oncogenic partners;[4,5] however, both alleles of the IgH gene may be involved in such translocation events.[4-6] In IIGMM one allele is involved in a productive rearrangement of the V-D-J genes allowing the production of a functional heavy chain whereas in light-chain MM the IgH gene is either in germline configu-

Table 1. Patient demographics.

	Patient 1	*Patient 2*	*Patient 3*
Stage at diagnosis	3B	1A	3A
IIG at diagnosis g/L	47 g/L (IgA-K)	35 g/L (IgG-L)	38 g/L (IgA-K)
UBJP at diagnosis	ND	ND	0.05 g/L (40% of UP)
ECOG score at diagnosis	2	1	2
Cytogenetics at diagnosis	ND	46XX	46XX
LDH at diagnosis NR (125 – 243 U/L)	83 U/L	230 U/L	221 U/L
β2-M at diagnosis NR (0.8 -2.2 mg/L)	4.2 mg/L	2.0 mg/L	4.0 mg/L
Creatinine at diagnosis NR (0.04-0.08 mmol/L)	0.10 mmol/L	0.04 mmol/L	0.05 mmol/L
Chemotherapy	CID x 4 (T1) In-Mel (T3)* M+P x 3 (T4)*	M+P x 12 (T1) VAD x 2 (T2) Hi-DEX x 3 (T3) CP (T4)	Hi-Dex x 4 (T1) DCEP x 1 (T3)*
Radiotherapy	Femur T6-T10, L5-S2	Sternum Pelvis	Humerus C5 – T5 Spine
HDT-SCT	Nil	Hi-Mel (T5)	Nil
Biological therapies	Thalidomide (11 months) (T2)	Thalidomide (11 months) (T6) Lenalinomide (8 months) (T7)*	Lenalinomide 2 months (T2)
Bisphosphonate	Clodronate Pamidronate	Clodronate Zolendronate	Zolendronate
Extramedullary disease after development of LEPP	Liver Paraspinal Perinephric Presacral retroperitoneum	Pulmonary Multiple subcutaneous Right para-nephric Pelvis	Epidural Pleural Multiple subcutaneous Left para-aortic
IIG at LEPP g/L	1 g/L (IgA-K)	1 g/L (IgG-L)	2 g/L (IgA-K)
SFLC at LEPP mg/L	6550 mg/L(κ)	605 mg/L(λ)	749 mg/L(κ)
Plasmablastic morphology	Yes	Yes	Yes
LDH at LEPP presentation (U/L)	765 U/L	349 U/L	607 U/L
β2-M at LEPP presentation (mg/L)	25.3 mg/L	6.7 mg/L	42.1 mg/L
Creatinine at LEPP presentation (mmol/L)	0.74 mmol/L	0.32 mmol/L	0.37 mmol/L
Survival duration after development of LEPP	5 months	10 months	5 months

*ND: not detected; UBJP: urinary Bence-Jones protein; ECOG: Eastern Cooperative Oncology Group; NR: normal range; T(n): therapy number; *: therapy given after LEPP development; LDH:lactate dehydrogenase; β2-M: β2-microglobulin; Hi-Dex: pulsed high dose dexamethasone; DCEP: dexamethasone, cyclophosphamide, etoposide and cisplatin; M+P: melphalan and prednisolone; VAD:vincristine, doxorubicin and dexamethasone; CP: low dose cyclophosphamide and prednisolone; CID: cyclophosphamide, idarubicin and dexamethasone; In-Mel:intermediate dose melphalan 25mg/m^2; Hi-Mel: high dose melphalan 200 mg/m^2; HDT- SCT: high dose chemotherapy and stem cell transplantation. For further details regarding the chemotherapy regime's see Kyle et al.*[9]

ration or has acquired illegitimate translocations of one or both alleles neither of which has the capacity to produce functional heavy chains.[5,6] The most plausible explanation for the lack of heavy chain secretion seen in LEPP is the accumulation of genetic mutations during clonal evolution that compromise the production of intact heavy chains. Mechanisms including lack of IgH mRNA transcription, instability or degradation of IgH mRNA or translation errors could underlie this loss of capacity.

Several investigators have demonstrated highly clonogenic cells in both peripheral blood and bone marrow that share immunoglobin gene sequences and idiotype specificity with the malignant plasma cells in patients with multiple myeloma.[7,8] These clonally related B cells might represent the proliferating fraction of MM and have increased resistance to chemotherapy.[8] Novel biological therapies such as thalidomide and lenalinomide are immunomodulators aimed at altering the stromal dependence of myeloma cells.[9] There have been numerous reports documenting increased extramedullary relapse and altered biological behavior following these therapies.[10,11] It is this environment of evolutionary pressure that is likely to engender the LEPP variant. In the context of targeted therapies, it is conceivable that LEPP represents a clonal expansion of those proliferative precursors that have not only acquired stromal independence but also lost the capacity to secrete IIG. Consequently LEPP manifests as plasmablastic cells with an extramedullary predilection that secrete only free light chains. Our cases represent the first documented series of this rare but clinically important mode of relapse. Whilst it is premature to suggest that all patients with IIGMM should be followed with serial SFLC measurements our cases emphasize the changing natural history of multiple myeloma in the era of biological therapies and further serve to highlight the role of SFLC assays in monitoring patients with IIGMM especially following these therapies.

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References

1. McIntyre OR. Laboratory Investigation of myeloma In: Myeloma Biology and Managemen. Oxford University Press, New York. 1995. p. 191-221.
2. Mead GP, Carr-Smith HD, Drayson MT, Morgan GJ, Child JA, Bradwell AR. Serum free light chains for monitoring multiple myeloma. Br J Haematol 2004;126:348-54.
3. Tate J, Mollee P, Gill D. Serum free light chains for monitoring multiple myeloma. Br J Haematol 2005;128:405-6.
4. Nishida K, Tamura A, Nakazawa N, Ueda Y, Abe T, Matsuda F, et al. The Ig heavy chain gene is frequently involved in chromosomal translocations in multiple myeloma and plasma cell leukemia as detected by in situ hybridization. Blood 1997;90:526-34.
5. Szczepanski T, van 't Veer MB, Wolvers-Tettero IL, Langerak AW, van Dongen JJ. Molecular features responsible for the absence of immunoglobulin heavy chain protein synthesis in an IgH(-) subgroup of multiple myeloma. Blood 2000;96:1087-93.
6. Magrangeas F, Cormier ML, Descamps G, Gouy N, Lode L, Mellerin MP, et al. Light-chain only multiple myeloma is due to the absence of functional (productive) rearrangement of the IgH gene at the DNA level. Blood 2004; 103:3869-75.
7. Matsui W, Huff CA, Wang Q, Malehorn MT, Barber J, Tanhehco Y, et al. Characterization of clonogenic multiple myeloma cells. Blood 2004;103:2332-6.
8. Rasmussen T. The presence of circulating clonal CD19+ cells in multiple myeloma. Leuk Lymphoma 2001;42:1359-66.
9. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med 2004;351:1860-73.
10. Raanani P, Shpilberg O, Ben-Bassat I. Extramedullary disease and targeted therapies for hematological malignancies--is the association real? Ann Oncol 2006[Epub ahead of print].
11. Balleari E, Ghio R, Falcone A, Musto P. Possible multiple myeloma dedifferentiation following thalidomide therapy: a report of four cases. Leuk Lymphoma 2004;45:735-8.
12. Bradwell AR, Carr-Smith HD, Mead GP, Tang LX, Showell PJ, Drayson MT, et al. Highly sensitive, automated immunoassay for immunoglobulin free light chains in serum and urine. Clin Chem 2001;47:673-80.