Oligoclonal reconstitution masquerading as myeloma relapse

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Dear Editor,

A 42-year-old lady was diagnosed to have International Staging System (ISS) stage II IgGλ myeloma in 2007. She achieved a minor response after VAD (vincristine, Adriamycin, dexamethasone) induction, then partial remission (PR) after further induction with VTD (bortezomib, thalidomide and dexamethasone), and finally immunofixation-negative complete remission (CR) after autologous stem cell transplantation (ASCT) in Dec, 2007, which was confirmed by bone marrow examination. (Figure 1A) She was maintained on thalidomide 50mg/day. Serial serum protein electrophoresis (SPE) remained negative until Dec, 2009 when SPE and immunofixation of serum (IFX) showed reappearance of IgGλ with the paraprotein level measuring 3.8g/L. However, she was completely asymptomatic and free of CRAB (hypercalcemia, renal failure, anaemia and bone disease) complications. Moreover, SPE showed that the "recurrent" IgGλ was in a different position on electrophoresis, (Figure 1B) and hence a diagnosis of oligoclonal reconstitution was made instead of disease relapse. In the absence of salvage chemotherapy, the low level of IgGλ paraprotein persisted between 3-4g/L until Oct, 2010 when repeat SPE and IFX showed disappearance of paraprotein. The patient remained in immunofixation-ve CR as of Oct, 2012.

We have reported frequent oligoclonal reconstitution, which was associated with superior event-free survival in myeloma patients. (Chim et al, 2010a) The paraproteins in oligoclonal reconstitutions often have an isotype different from the original paraprotein. (Mark et al, 2008) Recurrence of a paraprotein of the same isotype as diagnosis after achievement of CR will raise the possibility of myeloma relapse, implicating subsequent salvage treatment. Moreover, possibility of relapse is especially valid when the

paraprotein emerged at 2 years after ASCT, and became measurable. However, when the "recurrent" paraprotein was reviewed, it occupied a different position on electrophoresis gel, and hence consistent with an oligoclonal reconstitution instead of relapse. Finally, this oligoclonal paraprotein level remained low, and eventually disappeared, thereby confirming an oligoclonal reconstitution instead of relapse.

A better way to confirm if the recurrent paraprotein of the same diagnostic paraprotein as part of disease relapse is to perform two-dimensional gel electrophoresis, which is not available in our institute. Moreover, the diagnosis of "relapse" might have triggered salvage treatment in some centers. Finally, as there are many on-going clinical trials in myeloma, the detection of relapse is an important end-point for event-free or progression-free survival analysis.

Oligoclonal reconstitution is becoming prevalent in this era of targeted therapy in myeloma as the depth of response has been increased. Oligoclonal reconstitution was first reported in patients achieving CR after ASCT prior to the advent of novel agents. (Zent et al, 1998) However, in myeloma patients receiving induction therapy with novel agents followed by ASCT, as many as 25% - 33% of patients were found to develop oligoclonal reconstitution. (Chim et al, 2010b; Fernández de Larrea et al, 2011)

In conclusion, oligoclonal reconstitution in myeloma is an important differential diagnosis to relapse, impacts important end-points such as CR in clinical trials, and obviates the inappropriate consideration of salvage therapy. It is essential to review the serum protein electrophoresis and immunofixation gels to confirm the status of remission.

References

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Legend

Fig 1A Shows the achievement of CR after ASCT, occurrence of oligoclonal reconstitution and finally complete resolution of oligoclonal reconstitution.

Figure 1B showed monoclonal IgG at diagnosis by immunofixation (upper left), resolution of M-protein at the time of complete remission (upper right), recurrence of a new monoclonal IgG of a different molecular size due to oligoclonal reconstitution (blue arrow) as compared with the monoclonal IgG at diagnosis (dark arrow) (lower left), and finally, complete resolution of the oligoclonal reconstitution (lower right).

Fig. 1A

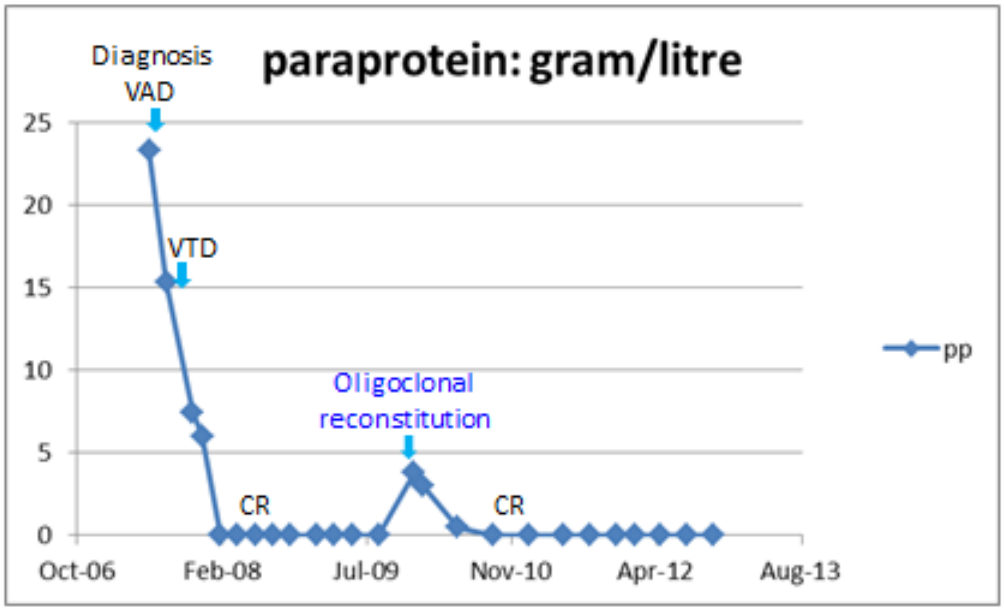
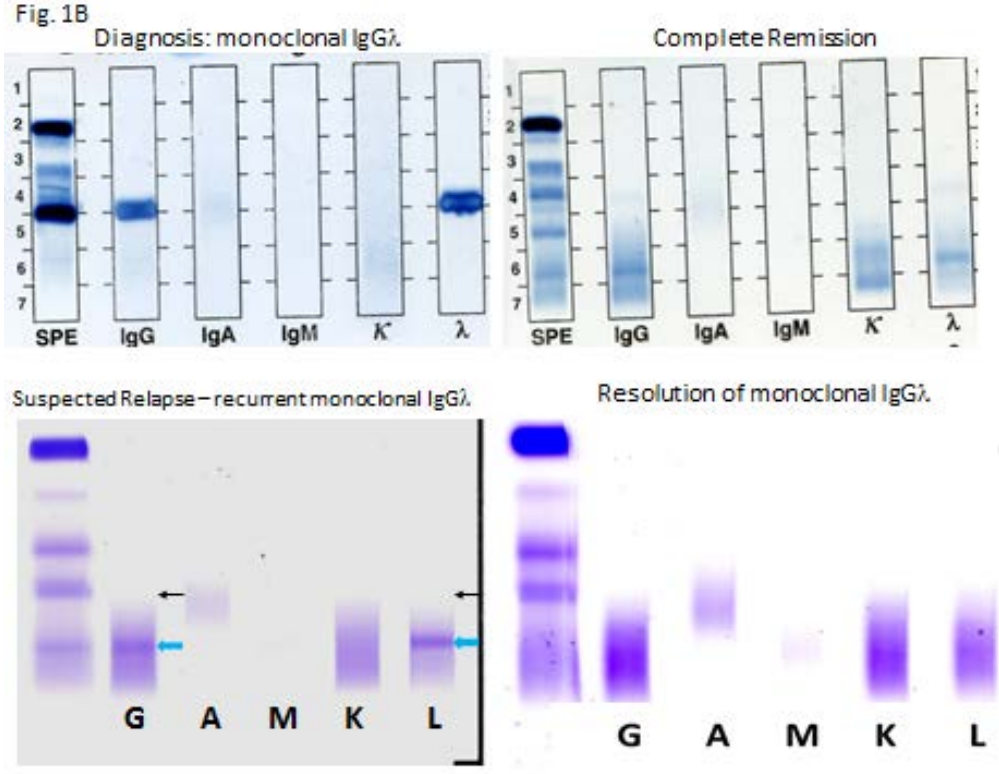

paraprotein: gram/litre
Diagnosis
VAD
VTD
Oligoclonal
reconstitution
CR
CR
25
20
15
10
5
0
Oct-06
Feb-08
Jul-09
Nov-10
Apr-12
Aug-13
pp

Fig. 1B


Diagnosis: monoclonal IgGλ
Complete Remission
SPE
IgG
IgA
IgM
κ
λ
Suspected Relapse – recurrent monoclonal IgGλ
Resolution of monoclonal IgGλ
G
A
M
K
L