

Secondary Monoclonal Gammopathy of Unknown Significance with Isotype Switching After CAR T-cell Therapy for Multiple Myeloma: A Case Report

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Background

Secondary monoclonal gammopathy of unknown significance (sMGUS) in multiple myeloma (MM) patients has been reported after stem cell transplantation (SCT) (autologous and allogenic), conventional chemotherapy, and novel anti-MM agents (1-4) . Interestingly, the results of many of these studies found an association between sMGUS and improved response, progression-free survival (PFS) and overall survival (OS). Only handful of reports have reported an emergence of sMGUS in Chinese population after CAR T-cell therapy (5, 6). Here, we report a case of sMGUS with appearance of distinct paraprotein peaks demonstrating isotype switching from IgA lambda to IgG lambda post-autologous CAR T-cell therapy and three-year follow up findings in an American and/or European population.

Case Description

A 66-year-old man was diagnosed with IgA lambda MM in October 2003. The patient had ISS-III disease with FISH demonstrating deletion 1p, gain of 1q, deletion 17p, trisomy 11, and trisomy 13. At the time of diagnosis serum paraprotein had two distinct peaks (paraprotein 1 and 2) with positive serum immunofixation for IgA lambda. From diagnosis until December 2019, the patient was treated with 18 lines of anti-MM therapy, including two ASCTs, PIs, iMiDs, an anti-CD38 antibody, etc. The response to these therapies varied, but none of them led to complete remission. After disease progression on the 18th line of therapy, the patient was enrolled in a clinical trial to receive *Idecabtagene Vicleucel* (Ide-cel) (NCT03601078). A total of 512.80 x 10^6 CAR T-cells were administered intravenously. Two months after CAR T-cell therapy, staging evaluation demonstrated a stringent complete remission (sCR) with negative minimal residual disease (MRD) by flow. At month 5 post-CAR T-cell therapy, the patient had reappearance of a paraprotein with two distinct peaks in the gamma region (paraproteins 3 and 4) with an IgG lambda isotype, which was different compared to the patient's pre-CAR T-cell therapy IgA lambda paraprotein (Figure). The original paraprotein peaks (paraproteins 1 and 2) in the gamma region were undetectable. The urine electrophoresis and immunofixation showed Bence-Jones (BJP) proteinuria (29 mg/24 hours) and lambda respectively. A bone marrow biopsy and aspirations revealed 1% polytypic plasma cells with continued MRD negativity. A whole-body PET-CT was also negative for any bony lesions or extramedullary plasmacytomas. Because the patient was asymptomatic without any clinical symptoms of myeloma progression, the patient was diagnosed to have sMGUS and followed under close observation without any active myeloma therapy. Three years post-CAR T-cell infusion, the patient remains asymptomatic and under observation. As shown in Figure, Paraprotein 3 has declined steadily since its initial appearance, now at 0.4 g/dL without therapy, further supporting that the reappearance of the IgG lambda paraprotein post-CAR T-cell was a sMGUS.

Results

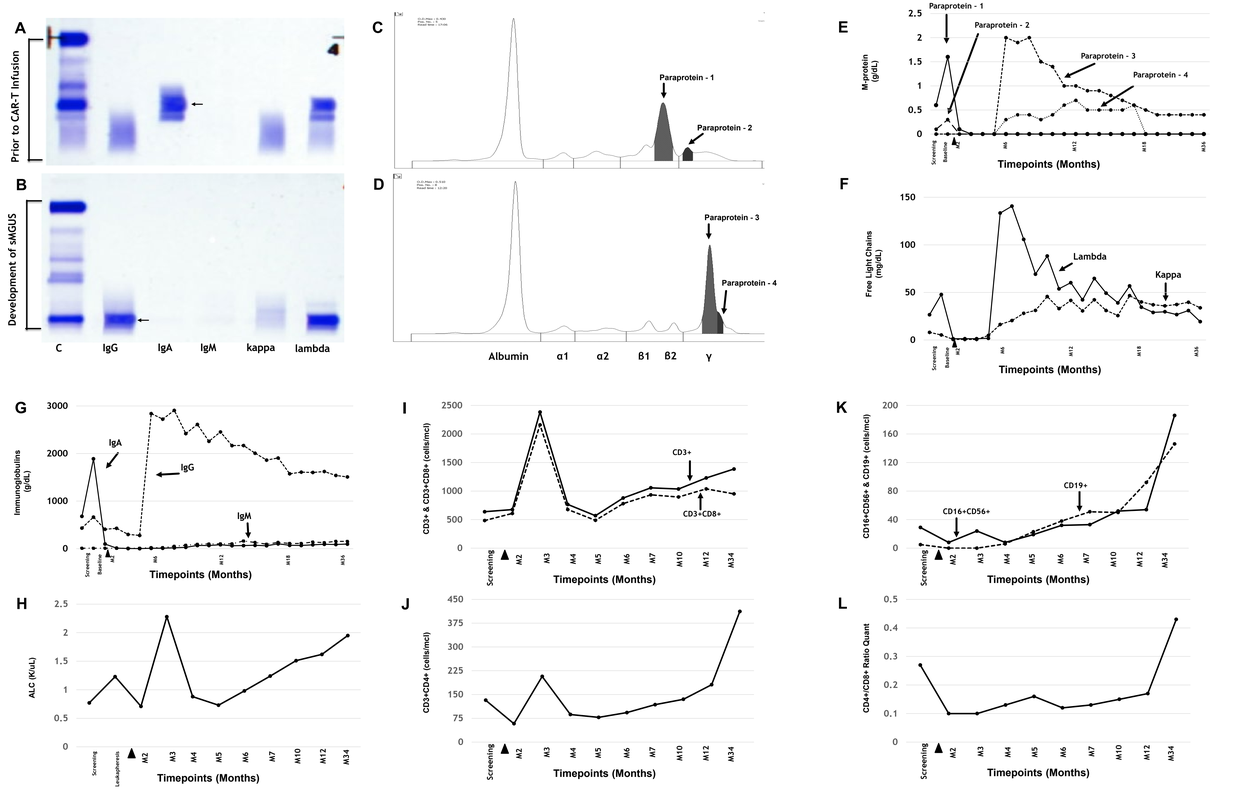


Figure. Biochemical assessment of M-protein, free light chains, Immunoglobulins, and lymphocyte subset counts at various timepoints. A & B: Serum Protein Electrophoresis prior to CAR-T therapy and at development of sMGUS. Distinct myeloma isotype IgA band prior to CAR-T therapy (A) disappeared with simultaneous appearance of distinct myeloma isotype IgG band at the time of sMGUS development (B). The free lambda light chain band remain distinct prior to as well as post CAR-T therapy (A & B). **C & D:** Serum protein electrophoretic pattern prior to CAR-T therapy and at development of sMGUS. The electrophoretic pattern shows paraprotein peaks 1 & 2 in β2 & γ regions respectively prior to CAR-T therapy (C). However, both of these paraprotein peaks were not discernible at the time of development of sMGUS simultaneously with emergence of new paraprotein peaks 3 & 4, both in new γ region (D). **E:** Quantitative presentation of M-protein. Measurable M-protein (Paraprotein 1 & 2) prior to CAR-T therapy were 0 g/dL at Month 3 Day 1 post CAR-T therapy suggesting remission which lasted for 3 months. However, M-protein started increasing but with two completely different peaks which are distinct from the original ones (Paraprotein 3 & 4). Both have been gradually declining leading to undetectable level of Paraprotein 4. **F:** Free light chains (kappa & lambda) level in serum. Robust recovery in lambda chain level post CAR-T followed by sharp increase in it's level with emergence of sMGUS. Later gradual decline in lambda chain level accompanied by gradual upward trend in kappa chain level with unknow significance. **G:** Serum level of Immunoglobulins A, G & M. Measurable IgA prior to CAR-T therapy is minimally measurable since Month 3 post CAR-T therapy while minimally measurable IgG prior to CAR-T therapy started increasing at the time of development of sMGUS suggesting switch in Myeloma isotype after CAR-T therapy. **H - L:** Absolute lymphocyte count, T cells (CD3+, CD4+, CD8+), NK cells (CD16+CD56+), B cells (CD19+), and CD4+/CD8+ ratio at different time points. Solid black upward triangle on x-axis suggest CAR-T infusion time point. (sMGUS = secondary monoclonal gammopathy of unknown significance, C = Control protein ladder, IgG= Immunoglobulins G, IgA= Immunoglobulins A, IgM= Immunoglobulins M, M= Month).

Clinical Practice Points

- A distinct paraprotein peak of an isotype different from the original paraprotein could develop as part of a phenomenon called sMGUS in patients with MM.
- Secondary MGUS in MM patients has been reported after stem cell transplantation (SCT), conventional chemotherapy, and novel anti-MM agents. Handful cases of sMGUS after CAR T-cell therapy are also reported in literature now.
- The patients with sMGUS without any symptoms or signs of disease progression could be monitored carefully and may not need MM-directed therapy.
- The pathophysiological mechanisms of the emergence of sMGUS is not understood properly but the recovery of B-cells, immune reconstitution, and changes in the BM microenvironment could be playing an important role.
- sMGUS with or without isotype switching and/or new paraprotein bands may be a rare but important example of a potentially benign and transient phenomenon representing pseudo-disease progression and also associated with longer progression-free survival and better overall outcomes. Careful clinical consideration is warranted to determine if a patient has benign sMGUS, which can be observed, or true disease progression that requires anti-MM therapy.

Conclusions

- To the best of our knowledge, this is the first case of sMGUS with isotype switching and distinct paraprotein bands following post-CAR T-cell therapy in an American and/or European MM population.
- Complete remission status may be associated with the emergence of sMGUS, which may correlate to longer PFS and better overall outcomes.
- Recovery of normal B-cells as part of the immune reconstitution process post-CAR T-cell therapy could contribute to the production of distinct paraprotein bands.
- Careful consideration is warranted to determine if a patient has a sMGUS, which can be observed, or true disease progression, which would require anti-MM therapy.
- This case suggests that those who develop sMGUS, especially with isotype switching and/or the development of new paraprotein peaks, may seem to have a transient and benign pseudo-progression of disease secondary to immune reconstitution post-CAR T-cell therapy.

References

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