IgG_1 MM. IgG_3 and IgG_1 have a propensity to form Ig complexes linked together by specific aggregating sites located in the Fd fragments of the immunoglobulin molecules.[6]

Cryoglobulins are proteins that precipitate or gel on cooling and dissolve when heated. Five percent of M-proteins are cryoglobulins.[7] However, the exact percentage of cryoglobulins in IgG_1 M-protein is not known. The presence of cryoglobulins causes purpura, cold urticaria, leg ulcers, gangrene of the toes, and symptoms of cold intolerance manifested by Raynaud's phenomenon.

The M-protein in this case was of IgG_1 kappa type. It formed a translucent gel at 4°C (*Figure 1*). The process of gelification was concentration- and temperature-dependent and was reversed by vortexing. The M-protein is not a typical cryoglobulin because it does not form a whitish precipitate that redissolves at 37°C. In fact, specific quantification of cryoglobulins revealed no significant levels even though three-fourths of the monoclonal protein was cryogelified. This was because the abnormal protein was completely redissolved during the washing process and discarded with the washing fluid.

As documented here, the process of reversible gelification can also erroneously lower the apparent paraprotein level and the corresponding serum viscosity if measured only from the top layers of the sample without previous vortexing (*Figures 2* and *3*). Clinically, it can cause misdiagnosis, inappropriate downstaging of the disease, or premature withdrawal of chemotherapy.

The mechanism of M-protein gelification-aggregation is unknown. Due to structural polymorphism, monoclonal immunoglobulins easily interact with one other. The reversible self-association may be explained by weak protein-to-protein binding. Aggregation probably involves a combination of dispersion forces,[8,9] hydrogen binding,[10] and hydrophobic interactions.[10] The dominant factors are unknown.

Similar phenomena have been noted in three other patients with IgM paraproteinemia at this institution. At present we have no clinical evidence that this unusual phenomenon could occur in vivo. The prevalence of the phenomenon is unknown. We feel that it is uncommon but, because of its significant clinical impact in the management of MM, every laboratory should look routinely for this phenomenon. We strongly recommend vortexing of all serum samples just prior to performing the relevant protein studies.

ACKNOWLEDGMENT

We acknowledge the technical assistance of Eva Madszar.

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Commentary

This article describes a laboratory phenomenon that can have significant clinical consequences. The authors report a case of a patient with multiple myeloma who has a gelifying IgG_1-kappa paraprotein. This gelification process was temperature- and concentration-dependent, and was reversed by vortexing.

The phenomenon of M-protein gelification has been observed in three other patients, and its mechanism is not understood. Although this phenomenon is uncommon, it can erroneously lower the measured paraprotein level and affect the serum viscosity. Thus it can affect the diagnosis and treatment of certain patients with multiple myeloma.

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