Pseudohypercreatininaemia in two patients caused by monoclonal IgM interference with enzymatic assay of creatinine

INTRODUCTION
Creatinine is released into the blood following non-enzymatic hydrolysis of creatine in skeletal muscle, and excreted into urine depending on glomerular filtration. The serum creatinine concentration is widely used as a marker of glomerular function because it increases in patients with decreased glomerular filtration rate (GFR). Although GFR is costly to measure, an estimated GFR (eGFR) can be calculated from the serum creatinine concentration. Since 2006, laboratories have calculated eGFR using the isotope dilution mass spectrometry traceable modiﬁcations.3 Enzymatic assays were later introduced, which are less susceptible to interference4 and more speciﬁc being unaffected by non-creatinine chromogens.5 Enzymatic assays were later introduced, which are less susceptible to interference4 and more speciﬁc being unaffected by non-creatinine chromogens.5 However, interference has been reported from 5-ﬂuorocytosine, ethamsylate, dopa-mine, dobutamine, nitromethane, creatine, sarcosine and ascorbic acid. Hummel et al.6 reported positive interference in enzymatic creatinine measurement caused by monoclonal IgM in three patients with Waldenström’s macroglobulinaemia. IgM can precipitate and interfere in the detection step of the reaction. This interference can be avoided by ultraﬁltration to remove protein before measuring creatinine. At the time of this publication, most clinical laboratories were measuring creatinine using alkaline picrate assays. However, since the introduction of eGFR, reporting the use of enzymatic assays has become more widespread. It, therefore, seems timely to illustrate this problem by describing two cases recently referred to the renal service.

CASE REPORT 1
A 71-year-old female was referred by her general practitioner (GP) to a satellite nephrology outpatient clinic for investigation of a serum creatinine of 257 μmol/L (Siemens Advia enzymatic assay). She was well, and there was no signiﬁcant past medical or renal history. She was not taking any prescribed medications, but did take evening primrose oil, cod liver oil, glucosamine and garlic capsules. Previous blood tests had shown normal glucose and bilirubin concentrations.

Initial investigations were all normal. However, capillary electrophoresis of serum proteins (Sebia UK), showed a discrete monoclonal peak at a concentration of 9 g/L. Immunofixation (Sebia UK) showed that this was IgM kappa. Most of the IgM present was monoclonal. No monoclonal free light chains were detected in the urine. To determine the cause of the increased serum creatinine, she was invited to the central renal unit for a renal biopsy. Prebiopsy blood tests showed a serum creatinine of 73 μmol/L (Abbott Architect 3 enzymatic assay), and a second specimen analysed by the same method showed a creatinine of 70 μmol/L. The apparent decrease in creatinine concentration was initially presumed to represent an episode of acute kidney injury (AKI), of unknown cause, from which, the patient had completely recovered. She was not biopsied.

Following discharge, she remained well, and after 2 weeks, attended the satellite nephrology outpatient clinic for review. The serum creatinine was again increased at 216 μmol/L (Siemens Advia enzymatic assay). To investigate the discrepancy in results, a serum specimen from the patient was sent to three different laboratories, and creatinine measured by three different methods viz Siemens Advia enzymatic assay, Abbott Architect 3 enzymatic assay and picric acid Jaffé (O’Leary) reaction. The results were as shown below in table 1.

<table>
<thead>
<tr>
<th>Method</th>
<th>Creatinine (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siemens Advia enzymatic assay</td>
<td>257</td>
</tr>
<tr>
<td>Abbott Architect 3 enzymatic assay</td>
<td>75/73</td>
</tr>
<tr>
<td>Picric acid Jaffé</td>
<td>82</td>
</tr>
</tbody>
</table>

GFR was measured deﬁnitively by iohexol clearance and found to be 63 mL/min/1.73 m². At this stage, it was clear that the serum creatinine concentration, as measured by the Siemens Advia enzymatic assay, was artefactually increased.

CASE REPORT 2
A 63-year-old male was referred by his GP to a different satellite general nephrology outpatient clinic for investigation of abnormal renal function. Serum creatinine had been above 300 μmol/L on two occasions (Siemens Advia enzymatic assays). There were no symptoms or signs of renal or systemic disease.

To further investigate this possible AKI, serum protein electrophoresis was performed, which showed an IgM kappa protein at a concentration of 15 g/L. Total IgM was increased at 20 g/L (0.5–2.0), and both IgA and IgG were low at 0.41 g/L (0.8–4.0) and 5.1 g/L (6.0–16), respectively. Capillary electrophoresis of serum proteins (Sebia UK) showed a discrete monoclonal peak. Immunofixation (Sebia UK) showed that this was IgM kappa. The IgM present was entirely monoclonal. Urine immunofixation detected free kappa monoclonal light chains. A bone marrow biopsy showed B cell lymphoma, in keeping with lymphoplasmacytic lymphoma. Subsequently, the patient attended the renal unit for a renal biopsy. However, prebiopsy blood tests showed creatinine 89 μmol/L (Abbott Architect 3 enzymatic assay). This was conﬁrmed by analysis of a second specimen, which showed creatinine 84 μmol/L.

A serum specimen was assayed simultaneously by Siemens Advia and Abbott Architect 3 enzymatic assays. The results were as shown below in table 2.

The discrepancy in creatinine measurements was further investigated by measurement of serum cystatin C concentration, which was normal at 0.90 mg/L (reference range <1.4). An eGFR calculated using cystatin C was normal at 105 mL/min/1.73 m². A renal biopsy was no longer considered necessary.

DISCUSSION
In both these cases, the Siemens Advia enzymatic assay consistently gave artefactually high creatinine results.

Table 1 Creatinine and eGFR results obtained from a single sample being analysed by three different methods—Siemens Advia and Abbott Architect 3 enzymatic assays, and picric acid Jaffé reaction

<table>
<thead>
<tr>
<th>Method</th>
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<td>Siemens Advia enzymatic assay</td>
<td>257</td>
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<td>Abbott Architect 3 enzymatic assay</td>
<td>75/73</td>
<td>&gt;60/60</td>
</tr>
<tr>
<td>Picric acid Jaffé</td>
<td>82</td>
<td>&gt;60</td>
</tr>
</tbody>
</table>

*eGFR, estimated glomerular filtration rate.*
Compared with the older, alkaline picrate methods, enzymatic assays for creatinine have less frequently been reported to be affected by interference, but there have been reports of interference by IgG and IgM. In the cases reported here, the discrepancies in creatinine concentrations resulted from pseudohypercreatininaemia, which we believe was caused by positive interference by monoclonal IgM. In the previously published cases, IgM concentrations ranged from 7.8 to 44 g/L, whereas the concentrations in the two cases reported here were both at the lower end of this range. This suggests that even low-level IgM paraproteinaemia, such as that present in monoclonal gamopathy of uncertain significance, can interfere significantly with some enzymatic assays. It is not known why this interference was confined to the Siemens Advia method, but other authors have observed that some paraproteins are susceptible to precipitation at a particular assay pH.

Given that IgM paraproteinaemia is not uncommon, and enzymatic assays are now widely used, clinicians are likely to encounter this interference. Pseudohypercreatininaemia caused by IgM paraproteinaemia should be considered when investigating the cause of an unexplained high serum creatinine concentration, so that inappropriate investigation and diagnostic conundrums can be avoided.

Table 2 Creatinine and eGFR results obtained from a single sample being analysed by two different enzymatic assays—Siemens Advia and Abbott Architect 3

<table>
<thead>
<tr>
<th>Test Method</th>
<th>Creatinine (μmol/L)</th>
<th>eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siemens Advia enzymatic assay</td>
<td>282</td>
<td>20</td>
</tr>
<tr>
<td>Abbott Architect 3 enzymatic</td>
<td>98</td>
<td>&gt;60</td>
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<tr>
<td>assay</td>
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*Abbreviations: eGFR, estimated glomerular filtration rate.*

REFERENCES


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