Original Paper

nephron Clinical Practice

Nephron Clin Pract 2009;111:c7–c11
DOI: 10.1159/000175798

Received: March 19, 2008
Accepted: July 3, 2008
Published online: November 22, 2008

Multiple Myeloma in Chronic Kidney Disease

Utility of Discretionary Screening Using Serum Electrophoresis

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Key Words
Myeloma · Serum electrophoresis · Chronic kidney disease

Abstract
Introduction: The incidence of multiple myeloma (MM) has increased in Scotland over the last 20 years. Approximately 25% of cases present directly to renal services. Serum electrophoresis is commonly included in the diagnostic screening tests performed in patients with chronic kidney disease (CKD). We examined the utility of serum electrophoresis in the population presenting to renal outpatient services in Glasgow. ***Methods:*** All new patient attendances at general nephrology clinics in the Glasgow renal units between 1/08/2004 and 31/07/2006, along with clinical data, were retrieved from the electronic patient records. Patients with acute kidney injury were excluded. All serum and urine electrophoresis requests and results for the same period were identified from Biochemistry and Immunology Laboratory Services. ***Results:*** A total of 2,544 new patients attended a renal clinic for the first time in the inception period, of whom 1,608 (63.2%) had serum electrophoresis tested. One patient with MM was identified, but the diagnosis was clinically apparent before the serum electrophoresis result was requested. A further 40 subjects had abnormal serum electrophoresis with mean paraprotein of 8.3 g/l (SD 6.1); none of these patients have subsequently developed MM, and the renal abnormalities are felt to be unrelated. This prevalence of monoclonal gammopathy of uncertain significance in 2.5% of the cohort is consistent with the expected prevalence in the general population. ***Conclusion:*** Our data demonstrate that serum electrophoresis in patients with CKD is not a useful screening test to identify MM.

Introduction

Renal disease in multiple myeloma (MM) most commonly presents as acute kidney injury [1]. In the acute setting, a diagnosis of myeloma is often suggested by other clinical findings or by renal biopsy investigating acute renal failure or heavy proteinuria. In relatively stable patients with chronic kidney disease (CKD), it is common practice to perform serum electrophoresis to detect and quantify a monoclonal protein band (paraprotein) as part of diagnostic screening. However, the utility of such screening in CKD is unknown.

The incidence of MM has increased in Scotland over the last 20 years [2]. Median survival from diagnosis is 2.3 years [2], and approximately 25% of cases present directly to renal services [1]. Impaired renal function is present in up to 50% of patients with MM at diagnosis [3], and is associated with shortened survival [4–7]. The de-

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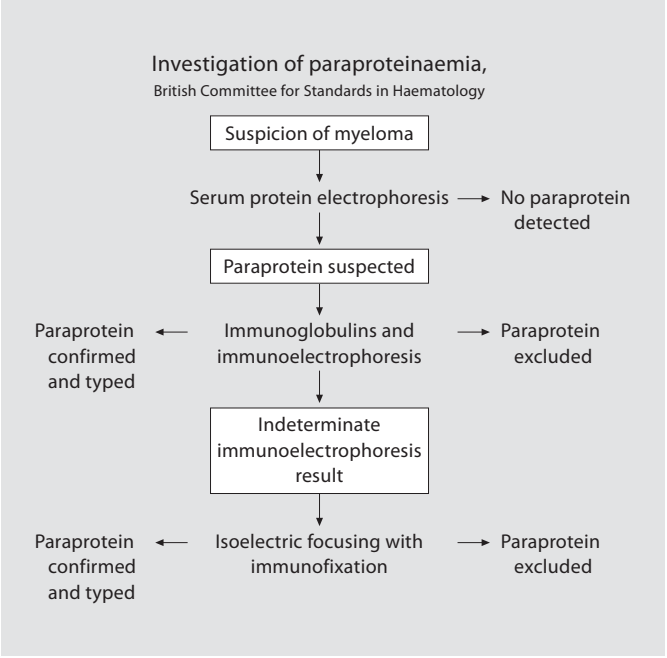

Fig. 1. Protocol for screening for plasma cell dyscrasias in the UK, by the British Committee for Standards in Haematology [12].

gree of renal failure at presentation is generally moderate and reversible in up to 50% of patients, particularly when it is related to precipitating factors such as hypercalcemia [8–11].

The British Committee for Standards in Haematology currently suggest a pathway of screening for the presence of paraproteins that is depicted in figure 1. The initial step is to perform serum and urine electrophoresis, progressing to immunoelectrophoresis and then to isoelectric focusing and immunofixation, in order to better define any suspected paraprotein identified [12].

The aim of this retrospective study was to determine the utility of electrophoresis as a screening test in the population presenting to renal outpatient services in Glasgow.

Methods

Patients attending all adult general nephrology clinics in Glasgow for the first time in the 2 year period from August 2004 to July 2006 were identified. Patients were mostly referred by general practitioners, with a minority being referred by other hospital specialists. The renal function, haemoglobin concentration (Hb), serum calcium, albumin and urine protein:creatinine ratio results from the first clinic visit were retrieved. Patients presenting with acute kidney injury, defined as a >50% rise in serum creatinine or requiring in-patient admission within 30 days of the first creatinine sample, were excluded. Patients who attended the renal clinic with previously diagnosed plasma cell disorders were excluded from the results (n = 11).

All serum and urine electrophoresis requests and results for the same time period were identified from Biochemistry and Immunology Laboratory Services in Glasgow. The serum proteins were separated by electrophoresis on agarose gels using the Sebia Hydrasys system. The individual fractions were stained using amido black, and quantitated by scan densitometry.

The cohort of patients seen at the clinic was matched against laboratory electrophoresis results using unique patient identification numbers. Serum free light chains were not part of the local routine diagnostic work-up. Very few of these tests were undertaken, and so were not included in this analysis.

The electronic patient record and case notes of patients who had detectable serum paraprotein were examined in detail to classify their plasma cell dyscrasia, according to the definitions of the International Myeloma Working Group [13]. In monoclonal gammopathy of undetermined significance (MGUS), the monoclonal protein is <30 g/l and the bone marrow clonal cells <10% with no evidence of MM, other B-cell proliferative disorders or amyloidosis. In asymptomatic (smouldering) myeloma the monoclonal protein is ≥30 g/l and/or bone marrow clonal cells ≥10% with no related organ or tissue impairment, which is typically manifested by increased serum calcium, renal insufficiency, anaemia, or bone lesions (CRAB) attributed to the plasma cell proliferative process. Symptomatic myeloma requires evidence of related organ or tissue impairment.

A list of all renal biopsies for the search period was matched against the list of all patients new to renal clinics. Text reports were searched for mention of myeloma or associated pathologies. All biopsies were examined by light, immunofluorescence and electron microscopy, and, if any features raised suspicion of nephropathy associated with plasma cell dyscrasia, then appropriate stains were performed.

Results

During the study period of August 2004 to July 2006, there were 2,544 new patient attendances at renal clinics. Patient demographics are shown in table 1. Of the patients, 1,608 (63.2%) had serum electrophoresis tested, of which 41 demonstrated a paraprotein, 40 subjects had a paraprotein concentration of less than 20 g/l and 93 subjects had immunofixation studies that included those showing a definite band on serum electrophoresis; the additional 53 studies being negative in those with a suspected monoclonal band on serum electrophoresis.

Only 81 subjects had urine electrophoresis performed, the results of which were normal.

Only 1 case of MM was identified. The case identified had clinical features of MM at the time of the first renal

Table 1. Characteristics of whole cohort and those who were or were not tested

	All clinic patients (n = 2,544)	Tested (n = 1,608)	Not tested (n = 936)	p
Age, years	61 ± 18.19	63 ± 16.3	59.7 ± 18.1	0.02
MDRD eGFR, ml/min/1.73 m^2	42 ± 23.4	42 ± 22	52 ± 27	<0.0001
Serum calcium (adjusted for albumin), mmol/l	2.32 ± 0.16	2.32 ± 0.16	2.33 ± 0.14	0.4
Hb, g/dl	12.65 ± 2.08	12.4 ± 2.1	12.9 ± 2.0	<0.0001
Urine protein:creatinine ratio, mg/mmol	61.5 ± 149	70 ± 151	45 ± 141	0.006

eGFR = Estimated glomerular filtration rate.

Table 2. Characteristics of the 1,608 patients who had serum electrophoresis

	Paraprotein (n = 40)	No paraprotein (n = 1,568)	p
Age, years	74.39 ± 9.4	63.0 ± 17.3	<0.0001
MDRD eGFR, ml/min/1.73 m^2	31.01 ± 15.1	42.37 ± 23.5	0.0009
Serum calcium (adjusted for albumin), mmol/l	2.29 ± 1.8	2.31 ± 1.6	0.59
Hb, g/dl	11.3 ± 2.4	12.4 ± 2.1	<0.0001
Urine protein:creatinine ratio, mg/mmol	153.6 ± 262	82.1 ± 166	0.014

clinic visit, as well as back pain, weight loss and hypercalcaemia, additional to an estimated glomerular filtration rate (eGFR) of 30 ml/min/1.73 m^2 and urine protein:creatinine ratio of 400 mg/mmol. No other patients have subsequently developed symptomatic MM, and are all therefore categorised as MGUS.

Of the 2,544 new patients, 137 (5.4%) underwent a renal biopsy, none of which showed any pathology suggestive of MM or related diseases. Of the 40 subjects with MGUS, only 1 (2.5%) had a renal biopsy. The biopsy was prompted by sustained proteinuria, and confirmed the clinical suspicion of diabetic nephropathy. No other subjects with MGUS required a renal biopsy.

Subjects who had electrophoresis requested for them tended to be older, with higher proteinuria and a lower eGFR (see table 1).

In the patients who were tested, those found to have a paraprotein tended to be older (63.0 vs. 59.7 years; p = 0.02) with a lower eGFR (31 vs. 42 ml/min/1.73 m^2; p = 0.0009), lower Hb (11.3 vs. 12.5 g/l; p = <0.0001) and more proteinuria (protein:creatinine ratio 154 vs. 82 mg/mmol; p = 0.014). There were no differences in serum calcium or albumin (see table 2).

Discussion

This is the first study that has reported the utility of selective screening of out-patients with reduced renal function and proteinuria to detect MM and associated conditions. We found that discretionary screening of 1,608 patients with evidence of renal disease in a 2-year period yielded only 1 case of MM. This patient had other clinical features (back pain and hypercalcaemia) at the time of first clinic visit that pointed to a diagnosis of MM. The incidence of MGUS in those tested in our study was 2.5%, which is similar to that expected in the general population.

There are no generally accepted guidelines on screening for MM, let alone in the context of CKD diagnostic evaluation. The UK National Kidney Federation and UK CKD guidelines recommend that 'patients with CKD should not be subjected to routine myeloma screening prior to referral' [14], although this statement is not backed by any evidence. Nevertheless, the available guideline was not fulfilled in the majority of patients with only 81 having had a paired urine sample for Bence-Jones protein estimation. Failure of urine sampling is a common problem, as has been reported in other series [15].

The only patient identified as having MGUS who had a renal biopsy in our study had a histological diagnosis of diabetic nephropathy only. It is possible that those who have not been biopsied have renal disease related to their MGUS, as monoclonal gammopathy can be associated with a wide variety of renal pathologies, including cast nephropathy, light chain deposition disease, AL amyloid deposition, dense deposit disease and fibrillary glomerulopathy. However, none of these patients have subsequently developed symptomatic MM. Furthermore, in a biopsy series of patients with monoclonal paraprotein, the majority had renal pathology unrelated to paraprotein [16]. Although individual cases of renal disease attributable to MGUS have been reported [17], our data suggest that the decision to perform renal biopsy should be guided by the presence of standard clinical indications relating to renal function and proteinuria.

Not all new patients attending the renal clinic had testing for serum electrophoresis. Those that were not tested were younger and had better renal function, implying that clinicians were screening selectively. Discretionary requesting of serum electrophoresisis common in UK. A recent local audit of 1,332 laboratory requests for serum electrophoresis [18] detected 72 patients with a paraprotein, but only 12 (<1%) cases of B-cell malignancies. However, that audit was restricted to subjects with a high globulin result prior to testing.

In our study, the age of the cohort who underwent discretionary testing is likely to account for much of the difference in eGFR and Hb between those who were tested and those who were not, as both eGFR [19] and Hb [20] tend to fall with age.

It is likely that clinicians decided not to request serum electrophoresis in young patients and those with minor renal abnormalities. This selection bias means that 2.5% is probably a slight overestimation of the prevalence of MGUS in patients attending renal clinics. Since only 1 patient was identified with MM, it seems unlikely that any secondary analysis would identify a high-risk group, in whom screening might be worthwhile. At first glance this may seem surprising as it is known that amyloidosis accounts for >10% of cases of nephrotic syndrome in patients >60 years of age [21]. However, we believe that serum electrophoresis is not a useful screening test in patients with nephrotic syndrome because most patients with nephrotic syndrome should have a renal biopsy irrespective of the serum electrophoresis result as many of the potential diagnoses for nephrotic syndrome are amenable to treatment (including AL amyloidosis).

Although serum electrophoresis is an inexpensive test, its utility is questionable. Strategies for using serum free light chain estimation to diagnose MM are superior, although their role in screening is uncertain.

Conclusion

Our results suggest that serum electrophoresis in non-proteinuric or nephrotic CKD is of limited value. The decision to perform serum electrophoresis in patients with CKD should be guided by the presence of other features of MM.

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