BMJ

BMJ 2012;344:e3033 doi: 10.1136/bmj.e3033 (Published 4 May 2012)

PRACTICE

RATIONAL TESTING

Investigating an incidental finding of a paraprotein

A paraprotein can have many causes—some serious but others unlikely ever to cause any problems. This article outlines key investigations and some of the difficulties that may arise after the incidental finding of a paraprotein

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

A 61 year old man with no significant medical history is found to have an elevated total protein and globulin level after routine private health screening in relation to his employment. He is referred to his general practitioner for evaluation. He reports being "completely well" other than occasional back pain and takes no regular medications. Further investigation with serum protein electrophoresis reveals that he has a paraprotein at a concentration of 21 g/L (any measured paraprotein is an abnormal finding)

What is the next investigation?

Raised serum globulin or total protein, or both, is often the first indication of the presence of a paraprotein. The level of globulin in the serum is derived by subtracting the albumin concentration from the total protein. All globulins are produced by plasma cells in the bone marrow. When a raised globulin level is found, it is important to determine the cause of the increased production of immunoglobulin:

- *Polyclonally increased plasma cells*—a reaction to several different disease processes including inflammation, infection, liver disease, and cancer

  or

- *Monoclonal proliferation of plasma cells*—resulting in a monoclonal immunoglobulin or paraprotein.

Serum protein electrophoresis or immunofixation

Serum protein electrophoresis and immunofixation are used to distinguish between polyclonal and monoclonal immunoglobulins (see figs 1⇓ and 2⇓). With the former, which is more common, the raised globulin may be accompanied by raised inflammatory markers and anaemia and should not trigger routine haematology referral. In the present case, however, the patient has been found to have a paraprotein on serum protein electrophoresis.

A paraprotein is not uncommonly identified during investigation of unrelated symptoms or after routine health screening, and most will be classified as monoclonal gammopathy of undetermined significance (MGUS). Identification of a paraprotein presents clinicians with the challenge of deciding whether and how far to investigate. MGUS can be detected in the serum of about 3% of people aged over 50, and most studies indicate that the incidence increases with age.[1]

MGUS is defined as the presence of a monoclonal protein (paraprotein) in the serum or urine of an individual with no evidence of myeloma, amyloid light chain amyloidosis, Waldenström's macroglobulinaemia, or related disorder (see table⇓) and no myeloma related organ or tissue impairment (box 1).[2] All listed criteria need to be met to make a diagnosis of MGUS.

The distinction between symptomatic myeloma and MGUS or asymptomatic myeloma depends on the presence or absence of myeloma related organ or tissue impairment, and the relevant criteria are shown in box 1. Patients with asymptomatic myeloma do not require immediate treatment but do have a higher risk of progression and should be followed by a haematologist.

On average the cumulative risk to an individual of transformation of MGUS to myeloma or other lymphoproliferative disorder is 1% a year, and the risk continues

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Learning points

- Raised serum globulin concentration or total protein may be the first indication of a paraprotein, but a raised globulin level is more commonly due to polyclonally raised globulins in reaction to inflammation, infection, or cancer
- A paraprotein is detected by serum protein electrophoresis and then further characterised by immunofixation
- Evaluate any patient with a newly detected paraprotein for symptoms or signs of myeloma or other lymphoproliferative disorder, both clinically and with investigations
- Most patients with a newly detected paraprotein will have monoclonal gammopathy of undetermined significance (MGUS) and will never progress to a condition that requires treatment

Box 1: Myeloma related organ or tissue impairment*

- Calcium concentration increased—Corrected serum calcium >0.25 mmol/L above the upper limit of normal or >2.75 mmol/L
- Renal insufficiency attributable to myeloma
- Anaemia—Haemoglobin 20 g/L below the lower limit of normal or <100 g/L
- Bone lesions—Lytic lesions or osteoporosis with compression fractures (magnetic resonance imaging or computed tomography may clarify)
- Other—Symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months)

*Adapted from International Myeloma Working Group[2]

even after 25 years.[3] Patients with myeloma or other lymphoproliferative disorder and those patients with MGUS with the highest risk of progression need to be identified and referred promptly to a haematologist. Conversely, it is important to identify patients with low risk MGUS so as to avoid over-investigating patients with a low risk of current or future serious disease.

Clinical evaluation

Patients with MGUS, by definition, do not have symptoms relating to their underlying diagnosis. However, it is important when a paraprotein is detected that the patient is formally evaluated for symptoms, signs, and abnormal test results suggestive of myeloma, lymphoma, or amyloid light chain amyloidosis (see box 2). If detected, further appropriate confirmatory laboratory investigations are required in addition to tests described below.

Further investigation

When a new paraprotein is detected, it would be considered normal practice for a laboratory to automatically carry out the following tests to further define the size and type of the paraprotein:

- *Paraprotein quantification*—Usually by densitometric measurement of the paraprotein band on serum protein electrophoresis (see fig 1⇓)

  A low concentration of paraprotein makes MGUS more likely, whereas a high concentration is more commonly associated with myeloma or Waldenström's macroglobulinaemia

  However, amyloid light chain amyloidosis is often associated with a low level paraprotein, and myeloma can also occur with a low paraprotein level

  The level of the paraprotein is also important in determining the risk of future progression once MGUS is confirmed (see below)

- *Definition of the immunoglobulin class* of the paraprotein by immunofixation (immunoglobulin heavy and light chain isotype)

  This is important as the type may direct future investigations. Myeloma is commonly associated with an IgG or IgA paraprotein, rarely IgD or IgE (see fig 2⇓). IgM paraproteins are more commonly associated with lymphoproliferative disorders such as Waldenström's macroglobulinaemia or low grade lymphoma

- In addition, the following laboratory and radiological tests should be carried out in all patients with a new paraprotein to exclude conditions in box 2 and (once these are excluded) to evaluate MGUS:

  Serum immunoglobulin levels to determine presence or absence of immune paresis (a reduction of residual normal immunoglobulin levels). This is important as low immunoglobulin levels in conjunction with recurrent bacterial infection are considered a "minor" criterion for the diagnosis of myeloma if other criteria are met

  Urinary protein estimation and urinary protein electrophoresis on a random urine sample to rule out a high urinary protein level suggestive of Bence Jones myeloma or nephrotic syndrome

  Full blood count

  Serum creatinine, urea, and electrolytes

  Serum calcium

  X rays of areas of skeletal pain.

The outcome

The patient is found to have an IgG κ paraprotein at a level of 21 g/L with normal serum immunoglobulin levels. There is a longstanding history of intermittent low back pain, physical examination was unremarkable, and investigations did not reveal anaemia, renal impairment, or hypercalcaemia (which might point to a diagnosis of myeloma). The urine was positive for Bence Jones protein at a low level. X ray of the lumbar spine shows mild degenerative changes only. The patient remains anxious.

Should this patient be referred?

MGUS is common, and primary care and other physicians often have difficulty in knowing which patients to refer to a consultant haematologist. The cumulative risk of progression (to multiple myeloma from IgG and IgA MGUS and to other malignant lymphoproliferative disorders from IgM MGUS) is about 1% a year. However, because of the high median patient age at the time of detection of a paraprotein and the existence of diseases not associated with the paraprotein, the risk that a patient with

Box 2: Symptoms, signs, and abnormal test results associated with myeloma, lymphoma, and amyloid light chain amyloidosis

Myeloma

- Bone pain
- Hypercalcaemia
- Renal failure
- Anaemia
- Hyperviscosity

Lymphoma and other lymphoproliferative disease

- Symptoms (such as night sweats, fever, weight loss)
- Lymphadenopathy
- Hepatosplenomegaly
- Hyperviscosity (especially if IgM paraprotein) resulting in, for example, headache, retinal vein engorgement
- Pancytopenia

Amyloid light chain amyloidosis

- Carpal tunnel syndrome
- Peripheral neuropathy
- Macroglossia
- Unexplained heart failure
- Nephrotic syndrome

MGUS will develop myeloma or related disorders in his or her lifetime is considerably lower.[3] Not all patients with MGUS need to be referred to a haematologist.

Criteria for referral and further investigation are set out in box 3. These referral criteria are based on strong associations with risk of progression.

- High level of paraprotein (>15 g/L if IgG or >10 g/L if IgA or IgM)[3]
- Paraprotein not of IgG class[3]
- Level of bone marrow plasma cell infiltration[4]
  Evaluation of bone marrow plasma cell infiltration requires referral to a haematologist
- Abnormal serum free light chain ratio[5]
  This relatively new serum assay for free light chain[6] detects levels of both κ and λ immunoglobulin light chains. A recent study has shown that patients with MGUS who have abnormal levels of or an abnormal κ to λ ratio of light chains in the blood are more likely to progress to active myeloma.[5] However, serum light chain levels are also raised in patients with renal impairment. This test should not be carried out in primary care or by general physicians except under the direction of a haematologist experienced in its interpretation. If advised, a request for serum free light chain assay should be made.

Importantly, variables such as the presence of Bence Jones proteinuria, immunosuppression, age, and sex have not been found to have predictive value for progression.[7]

Based on data from a number of studies, a simple risk stratification model for progression has been proposed for use by haematologists that entails measurement of the size and type of paraprotein and of the serum free light chain ratio.[5]

The patient is referred in view of his relatively high paraprotein, chronic back pain, and anxiety. Further investigations show that he has a normal serum free light chain ratio, bone marrow plasma cell infiltration <5%, and normal skeletal survey, confirming that he does not have myeloma.

What happens next?

There are no definite rules regarding follow-up of MGUS, but guidance is based on the estimated risk of progression.[8 9]

This patient is reassured that there is no evidence of myeloma or other lymphoproliferative disorder. He is advised that, although MGUS can progress to a malignant condition, the overall risk of progression is relatively low at around 20% over 20 years.[3] The condition does not require active treatment, but rather a "watch and wait" approach. His own risk of progression based on the risk stratification model is "low intermediate," so lower than the "average" for all patients with MGUS, providing some further reassurance.

The patient is referred for follow-up to an outreach service designed to use local phlebotomy services with central haematologist review of laboratory parameters and symptoms identified by a self assessment questionnaire. (This is an increasingly popular follow-up model in the UK designed to reduce the burden of follow-up on primary care physicians and avoid unnecessary haematology clinic visits while allowing some specialist input.[10]) He and his general practitioner are given information sheets that include details of symptoms that might trigger a re-referral (such as fatigue, recurrent infections, unexplained bleeding, bone pain, weight loss). It is recommended that blood tests for paraprotein level, full blood count, serum creatinine, urea, electrolytes, and corrected serum calcium be carried out every three months initially, with the interval extending to six or 12 months if results remain stable and no symptoms are reported.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationship with any organisation that might have an interest in the submitted work in the previous three years; JMB chairs the guideline committee of the UK Myeloma Forum and is a member of the British Committee for Standards in Haematology, and has received honorariums from Celgene, Novartis, Janssen, and Pfizer for talks at conferences, membership of advisory boards, and chairing symposiums or trial steering group meetings in

Box 3: Which patients with a paraprotein should be referred for specialist review

- Symptoms or signs of myeloma or lymphoproliferative disorder
- Unexplained blood test or x ray results (such as raised creatinine or calcium concentrations)
- IgG paraprotein >15 g/L
- IgA or IgM paraprotein >10 g/L
- IgD or IgE paraprotein at any level (rare)

relation to the treatment of myeloma and guidelines for the investigation and treatment of myeloma.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent not required (patient anonymised, dead, or hypothetical).

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Cite this as: *BMJ* 2012;344:e3033

Table

Table 1| Diagnostic criteria for monoclonal gammopathy of undetermined significance (MGUS), asymptomatic myeloma, and symptomatic myeloma*

MGUS	Asymptomatic myeloma	Symptomatic myeloma†
Paraprotein in serum <30 g/L	Paraprotein in serum >30 g/L *or*	Paraprotein in serum or urine‡
Bone marrow clonal plasma cells <10%, low level of plasma cell infiltration in a trephine biopsy (if done)	Bone marrow clonal plasma cells >10%	Bone marrow (clonal) plasma cells
No myeloma related organ or tissue impairment (including bone lesions or symptoms)	No myeloma related organ or tissue impairment (including bone lesions or symptoms)	Myeloma related organ or tissue impairment (including bone lesions or symptoms)
No evidence of other B cell lymphoproliferative disorder or amyloid light chain amyloidosis or other light chain, heavy chain, or immunoglobulin associated tissue damage§		

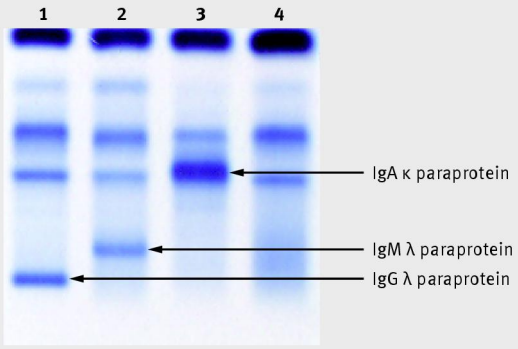
*Adapted from International Myeloma Working Group.[2]

†Patients without symptoms but with significant myeloma related organ damage are grouped with symptomatic myeloma because of the need for treatment.

‡No specific level required for diagnosis. A small percentage of patients have no detectable paraprotein in serum or urine but do have myeloma related organ or tissue impairment and increased bone marrow plasma cells (non-secretory myeloma).

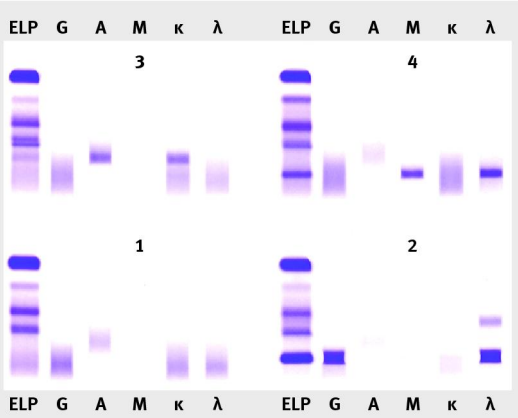
§Amyloid light chain amyloidosis and the neurological syndromes related to IgM paraprotein are examples of monoclonal gammopathy associated with specific syndromes.

Figures



Lane 1 shows an IgG λ paraprotein of 7 g/L
Lane 2 shows an IgM λ paraprotein of 8 g/L
Lane 3 shows an IgA κ paraprotein of 28 g/L
Lane 4 shows normal polyclonal immunoglobulins

Fig 1 Serum protein electrophoresis showing examples of patients with a paraprotein and normal polyclonal immunoglobulins



Panel 1 is normal serum with polyclonal immunoglobulins
Panel 2 is serum with high level of IgG λ monoclonal immunoglobulin with monoclonal λ free light chains and little polyclonal immunoglobulin; the patient had myeloma with renal failure
Panel 3 is serum with low concentration IgA κ paraprotein
Panel 4 is serum with IgM λ paraprotein

Fig 2 Four serum samples processed for immunofixation. In each panel the same serum has migrated along six tracks that have then been stained for protein (ELP); for IgG, IgA, or IgM heavy chains; or κ or λ light chains