Cases in primary care laboratory medicine

Paraprotein management

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This article explores best practice in the investigation and monitoring of paraprotein bands in blood or urine. It looks at the pitfalls and provides a summary of guidance

We present two cases illustrating the use of electrophoresis in the diagnosis and monitoring of plasma cell dyscrasias. The presence of monoclonal protein bands (paraproteins) in myeloma is well recognised; other conditions in which paraproteins may be seen are less well understood, as is the relatively common monoclonal gammopathy of unknown significance (MGUS) often previously referred to as benign paraproteinaemia.

Case 1

A 58 year old woman was referred urgently to hospital with a three month history of lethargy, weight loss, dysphagia, and nausea. On the day she was seen by her general practitioner she was weak and hypotensive (90/58 mm Hg). Examination showed an underweight woman (body mass index 19) with a blood pressure of 90/60 mm Hg, pulse 90 beats per minute, muscle wasting, no oedema, and no focal neurological signs.

Results of initial laboratory investigations were sodium 128 mmol/l, potassium 5.2 mmol/l, urea 7.2 mmol/l, creatinine 105 μ mol/l, total protein 52 g/l, albumin 27 g/l, aspartate transaminase 68 IU/l, alanine transaminase 86 IU/l. Serum immunoglobulins IgG, IgA, and IgM were within the reference range.

A short synacthen test produced blood cortisol concentrations of 254 mmol/l at 0 minutes and 316 mmol/l at 30 minutes. She was given replacement steroids and began to improve.

Investigation of her low serum albumin showed proteinuria (total protein excretion 8.2 g/24 hours). Serum electrophoresis showed no visible paraprotein band, and a subsequent immunofixation was negative. Urine electrophoresis showed a dense albumin band and one additional band, typed by immunofixation as kappa light chains (600 mg/l).

She was referred for nephrology assessment. Serum amyloid component P (SAP) scintigraphy showed heavy amyloid load in spleen and liver. In view of these findings a renal biopsy was not performed, and she was diagnosed as having primary amyloidosis (AL amyloidosis). She was treated with melphalan and dexamethasone.

Summary points

The presence of a serum paraprotein band is not diagnostic of myeloma

Monoclonal gammopathy of unknown significance (MGUS) is a common explanation for low concentration paraprotein bands and requires follow-up

Urine and serum electrophoresis should be performed for suspected plasma cell dyscrasia

Paraprotein bands can be associated with other non-myeloma disease, including amyloid lymphoma, leukaemia, infection, and chronic inflammatory disease

Absence of paraprotein bands does not include plasma and dyscrasia

This is the second article in this series

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Case 2

A 72 year old woman was referred to her local haematology outpatient clinic for investigation of a normocytic anaemia (haemoglobin 98 g/l) with normal blood film, identified from a full blood count requested when she attended her general practitioner with a recent chest infection.

When seen, she was clinically anaemic, appeared otherwise in good health, and reported no specific symptoms. Two episodes of upper productive respiratory tract infection in the previous three months had both responded to antibiotics.

Laboratory investigations showed an anaemia of 101 g/l, neutrophil count of 1.9×10^9 /l and platelet count of 110×10^9 /l, plasma viscosity of 2.25, and serum calcium (corrected) 2.83 mmol/l. Renal function was unremarkable for age (serum urea 6.8 mmol/l, creatinine 98 μ mol/l), and urine was negative on dipstick testing.

Serum total protein was 78 g/l, albumin was 38 g/l, serum IgG was 36 g/l, and both IgA and IgM were suppressed (< 0.2 g/l). Serum protein electrophoresis

What follow-up is required once a patient has been found to have a paraprotein band?

- Initially 3-6 month electrophoresis for IgG, IgA, or IgM bands of less than 15 g/l in patients without signs or symptoms
- Annual electrophoresis thereafter for stable IgG, IgA, or IgM bands of less than 15 g/l, where there are no accompanying indicators for a plasma cell dyscrasia
- Referral to a haematologist for IgA or IgG bands > 15 g/l or IgG, IgA, or IgM bands < 15 g/l with accompanying indicators for a plasma cell dyscrasia and other Ig bands (IgE and IgD are rare)
- Immediate tests after initial identification of a monoclonal band: full blood count, calcium, and renal function

What are the uses of serum immunoglobulins and electrophoresis?

Serum immunoglobulins should be measured and an electrophoresis performed:

- As part of the primary screen for suspected plasma cell dyscrasias (myeloma, lymphoma, chronic lymphatic leukaemia, heavy chain disease, amyloid)
- As part of the diagnostic investigation of suspected primary and secondary immunodeficiency—that is, patients with recurrent documented infections

They are of secondary value in the investigation of:

- Liver disease
- Connective tissue disease
- Sarcoidosis
- Chronic infection

showed a paraprotein band, typed by immunofixation as IgG kappa and measured by densitometry to be 33 g/l. Urine electrophoresis showed no monoclonal band.

Magnetic resonance imaging showed diffuse bony lesions consistent with myeloma and the patient's bone marrow biopsy contained 34% plasma cells.

Her laboratory records showed that a protein electrophoresis had been done four years earlier. It contained a paraprotein band of 4 g/l, typed as IgG kappa at the time of an unrelated hospital admission, described in the discharge summary as probable benign paraproteinaemia. Her blood count at that time had been unremarkable and no follow-up samples had been taken.

Discussion

These two cases illustrate the utility of serum and urine protein electrophoresis in investigating and monitoring diseases associated with paraproteins. Paraproteins may be present in blood or urine, or both, and may be absent in plasma cell dyscrasias. They are found in a range of inflammatory and infectious diseases associated with polyclonal increases in γ globulins. If they are caused by infection, the bands will disappear after effective treatment and do not indicate myeloma.^{1,2} If they are not associated with a polyclonal increase in γ globulins, their presence in blood, particularly in small quantities, may not be clinically important (monoclonal gammopathy of unknown significance, MGUS) or may be associated with other diseases, including amyloidosis, leukaemia, lymphoma, and infectious and inflammatory diseases, or may occur as an incidental finding.

MGUS

MGUS is found in about 1% of people over 50 years old and in 3% of those over 70 years old.³ Paraprotein concentrations over 20 g/l (IgG) or 10 g/l (IgA)⁴—particularly when associated with Bence Jones proteins (free light chains) in urine, anaemia, bone fracture or bone pain, suppression of other immunoglobulin classes, and renal impairment—are more likely to reflect myeloma, although the diagnosis is based on an increase in plasma cell content in bone marrow.

About 1.5% of cases of MGUS per year progress to myeloma,⁵ and annual follow-up with electrophoresis and densitometry is recommended to detect increasing concentrations of paraprotein as an indicator of the possible progression towards myeloma,¹ in order to guide the decision to investigate further and begin treatment. Failure to monitor patients will expose those few who do progress to risks of infection, hypercalcaemia, and pathological fracture or renal dysfunction.

Free light chains

Free light chains are nephrotoxic, and their presence in urine is associated with renal disease both in primary amyloidosis and myeloma. They are not reliably detected by urine test strips.^{1,5,6} As they may be present in patients with myeloma irrespective of whether a serum paraprotein is present, urine electrophoresis is an essential adjunct to serum electrophoresis in investigations of possible plasma cell dyscrasia.^{1,7} Immunofixation appearances similar to those of free light chains (light chain ladders) may also be seen in urine in inflammatory disease in elderly people.⁸

Primary amyloidosis is a rare cause of nephrotic syndrome. It is caused by a plasma cell dyscrasia producing widespread organ deposition of amyloid AL protein, which is formed as a result of monoclonal light chain production.

In case 1, the light chains were identified as part of the investigation of nephrosis. Amyloid was suggested by the coexistence of Addison's disease and confirmed by serum amyloid P component (SAP) scintigraphy.

What are the sources of evidence?

A review of best practice published in the *Journal of Clinical Pathology* indicates the varying degrees of evidence that back up these recommendations.⁹ The

Useful websites

See first article in this series (8 July, p 83) for a list of general websites

International Myeloma Organization (UK)
www.myeloma.org.uk—Information for patients and professionals on myeloma and links to related topics

guidance on use of serum electrophoresis and monitoring of paraprotein bands is based on observational studies. The recommendation to include urine electrophoresis when investigating possible plasma cell dyscrasias is based on evidence of the limited performance and numbers of false negative diagnoses when serum electrophoresis is used alone.

There is little evidence that monitoring for established paraprotein bands in patients with MGUS influences outcome. Although there is no evidence that early treatment of low grade so called smouldering myeloma delays the onset of active disease, early treatment can reduce the development of bone disease and the guidance to monitor patients with MGUS would seem logical on these grounds. The monitoring intervals recommended are based on consensus guidance; no studies are available on the influence of longer or shorter monitoring intervals on outcome.

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- 1 Keren DF, Alexanian R, Goeken JA, Gorevic PD, Kyle RA, Tomar RH. Guidelines for clinical and laboratory evaluation of patients with monoclonal gammopathies. *Arch Pathol Labor Med* 1999;123:106-7.
- 2 Riches P. Paraproteinaemias. In: Marshall WJ, Bangert SK, eds. *Clinical biochemistry*. Edinburgh: Churchill Livingstone, 1995:493-506.
- 3 Kyle R. Monoclonal gammopathy of undetermined significance and solitary plasmacytoma. *Hematol Oncol Clin North Am* 1997;11:71-87.
- 4 UK Myeloma Forum. Guidelines on the diagnosis and management of multiple myeloma. *Br J Haematol* 2001;115:522-40.
- 5 Alexanian R, Weber D, Liu F. Differential diagnosis of monoclonal gammopathies. *Arch Pathol Labor Med* 1999;123:108-13.
- 6 Keren DF. Procedures for the evaluation of monoclonal immunoglobulins. *Arch Pathol Labor Med* 1999;123:126-32.
- 7 Graziani M, Merlini G, Petrini C. IFCC Committee on Plasma Proteins, SIBioC Study Group on Proteins. *Clin Chem Lab Med* 2003;41:338-46.
- 8 Beetham R. Detection of Bence Jones protein in practice. *Ann Clin Biochem* 2000;37:567-70.
- 9 Smellie WSA, Wilson D, McNulty CAM, Galloway MJ, Spickett GA, et al. Best practice in primary care pathology: review 1. Best Practice Working Group. *J Clin Pathol* 2005;58:1016-24.

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St John's wort, a panacea?

When my father's GP surgery was ransacked in 1978 during the communal riots in Sri Lanka's sadly beautiful hill capital, Kandy, I went to pick up the pieces and found this bottle with some of the tincture still left. Almost as a reflex, I picked it up and brought it with me when I came to England. Now it occupies a prominent position in my personal library of 3000 rare and old medical volumes as a nostalgic (from the Greek *nostos*, return home, + *algos*, pain) object. My father's surgery was first established in the late 1940s, and I have no idea if he used the tincture as a treatment or if it was a legacy from an earlier practice that he bought.

The practice of hanging St John's wort outside the front door to protect from lightning was known for several centuries. In medieval times people believed that if you slept with a branch of it under your pillow on St John's Eve (the night before St John's Tide), the saint would appear in a dream, give his blessing, and prevent you from dying during the following year.

The ancient Chinese used its leaves, seeds, and bright yellow flowers for treating diseases. Another species of the same genus—*Hypericum androsaemum*, known as St Peter's wort—was used as a mild purgative

and was recommended by ancient Roman herbalists and physicians including Dioscorides and Galen. Chappan Harris's *Medical Dictionary* (1884) mentions its use as an anodyne (pain killer). Matthew Robinson's *Family Herbal* (1889) gives additional uses for flow of urine, vulnerary (venereal disease), falling sickness, sciatica, and palsy.

In his physical dictionary published in 1708, Stephen Blancard or Blanchard, a professor of history at Middlesbrough who became a physician at Franeker in the Netherlands, has an entry on St John's wort, describing it as, "an excellent diuretic and vulnerary herb; a decoction of it cures Tertian agues and Quartans; it stops spitting of blood, and expels gravel; a tincture of the flower is excellent in mania, and the flowers infused in Spirit of Wine kill worms; the compound of this herb is much used; it is excellent for bruises and aches, and for spitting of blood."

Few herbs have been used in such a wide variety of diseases. In addition to its role as an anthelmintic, analgesic, anti-inflammatory, diuretic, anti-haemorrhagic, antimalarial, antiepileptic, and laxative, it has also been used in sexually transmitted diseases, nerve palsies, and mania.

Its present revival in treating depression has restored a little of its glory. When I smell the strong odour from the remaining tincture I wonder if it holds other virtues that we have not yet explored.

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