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CORE TRAINING FOR DOCTORS

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Paraproteinaemia

Introduction

A paraprotein is a monoclonal immunoglobulin or immunoglobulin light chain which is detected in the blood or urine. It arises from the clonal proliferation of mature B cells, usually plasma cells or B-lymphocytes. Paraproteins are characterized by a homogenous electrophoretic migration and the expression of a single light chain type, either kappa or lambda. A raised paraprotein level can occur secondary to malignant B-cell disorders, most commonly multiple myeloma, or monoclonal gammopathy of uncertain significance, in which the detected paraprotein is at a low level. Paraproteinaemia can also occur in other malignant conditions. This article helps the general physician to know when to request serum and urine electrophoresis, which conditions are associated with a paraprotein, and the differences between multiple myeloma and monoclonal gammopathy of uncertain significance.

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How often are paraproteins detected in the general population?

Paraproteins are commonly found in general medicine, and are associated with increasing age. Large population-based studies have established that 3.2% of individuals over the age of 50 years have a detectable paraprotein (rising to 5% over the age of 70 years) (Kyle et al, 2006). The incidence varies with age, sex and ethnicity, being a more common finding in the elderly, males and Afro-Caribbean populations.

The majority of these patients will be diagnosed with monoclonal gammopathy of uncertain significance and will not require any treatment. A small proportion will be diagnosed with myeloma or another condition that will require treatment.

Disorders associated with a paraproteinaemia

A paraproteinaemia is associated with many clinical conditions (*Table 1*). Based on a review of more than 1000 patients from the Mayo Clinic, the most common diagnoses made following the finding of a raised paraprotein level are: monoclonal gammopathy of uncertain significance (51%) and multiple myeloma (18%); the remainder include those with asymptomatic or smouldering myeloma, lymphoproliferative disorders and AL amyloidosis (Kyle and Rajkumar, 2006). Myeloma and

Table 1. Disorders associated with a paraprotein

Malignant B-cell disorders	Multiple myeloma
	Solitary plasmacytoma (bone or extramedullary)
	Lymphoproliferative disorders (lymphoplasmacytic lymphoma, chronic lymphocytic leukaemia)
	AL amyloidosis
	Heavy chain disease
	POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma-proliferative disorder, Skin changes)
Monoclonal gammopathy of uncertain significance	
Non-malignant systemic disease	Autoimmune disease,e.g. rheumatoid
	Cutaneous disease, e.g. pyoderma gangrenosum
	Chronic liver disease
	Infections, e.g. tuberculosis, infective endocarditis

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monoclonal gammopathy of uncertain significance are discussed in more detail later.

A paraprotein can occasionally be found in other haematological malignancies such as an underlying lymphoproliferative disorder, for example chronic lymphocytic leukaemia or lymphoplasmacytic lymphoma. In this instance, clinical and laboratory features usually facilitate the diagnosis and differentiate them from myeloma or monoclonal gammopathy of uncertain significance. Of note, lymphoplasmacytic lymphoma (a rare type of non-Hodgkin's lymphoma) is characterized by a circulating IgM paraprotein, bone marrow failure, lymphadenopathy and organomegaly, and occasionally peripheral neuropathy. High circulating levels of IgM paraprotein can also lead to hyperviscosity with potential adverse consequences such as a stroke. Paraproteins may also be associated with type I and II cryoglobulinaemia.

Low paraprotein levels may be associated with non-malignant systemic disorders. Examples include autoimmune disorders (e.g. rheumatoid arthritis, scleroderma), chronic liver disease and atypical infections. These patients have monoclonal gammopathy of uncertain significance and may require treatment for the systemic disorder (Cook and Macdonald, 2007).

Table 2. Clinical indications for testing for paraproteinaemia

Bone disease (persistent back pain, osteopenia, lytic bone lesions)
Unexplained impaired renal function
Normochromic normocytic anaemia +/- pancytopenia
Hypercalcaemia
Recurrent bacterial infections
Hyperviscosity
Nephrotic syndrome
Unexplained peripheral neuropathy

When should one test for paraproteinaemia?

Patients with suspected myeloma or other B cell malignancies should be investigated for a paraprotein. Therefore, it is reasonable to screen for the presence of paraproteinaemia in patients with any of the clinical findings listed in *Table 2*.

It is important to request both serum protein electrophoresis and urinary protein electrophoresis to identify Bence Jones protein. Screening both the blood and the urine increases the ability to detect a paraprotein. In 15% of myeloma patients, the paraprotein is present only in the urine. Serum free light chain analysis can also be used to detect light chains, but this is not routinely required as a screening tool.

Who should be referred to haematology and how quickly?

For those individuals with a paraprotein, the main issue is to distinguish between symptomatic myeloma, asymptomatic or smouldering myeloma and monoclonal gammopathy of uncertain significance. Referral to haematology is appropriate to answer this question. The urgency of referral depends on the clinical situation: emergency inpatient assessment is required if there are features of medical emergencies associated with myeloma (e.g. renal failure, hypercalcaemia, cord compression, hyperviscosity); if a raised paraprotein level is found and myeloma is strongly suspected from the clinical history, then an urgent outpatient referral is required indicating suspected cancer and review within 2 weeks; if a paraprotein is found routinely, especially if it is low level and without any concerning features, then a non-urgent outpatient referral is appropriate.

What is the difference between monoclonal gammopathy of uncertain significance, asymptomatic and symptomatic myeloma?

Monoclonal gammopathy of uncertain significance is a pre-malignant condition associated with a low level paraprotein, low level plasma cell infiltrate in the bone marrow, and no organ damage to suggest myeloma. There is a small risk of progression to myeloma (1% per year) (Kyle et al, 2006). Patients with myeloma have an excess of plasma cells in the bone marrow, or a paraprotein of at least 30 g/litre. Those who are otherwise well have asymptomatic myeloma (i.e. no evidence of organ damage) and require no treatment, while those with organ damage have symptomatic disease and require treatment.

The diagnostic criteria are listed in *Tables 3* and *4*. It is important to establish whether the organ damage is myeloma related, rather than related to another condition. For example patients may have renal impairment as a result of hypertension, or vertebral collapse secondary to osteoporosis, rather than myeloma.

Monoclonal gammopathy of uncertain significance: prognosis and management

It is difficult to predict who will progress from monoclonal gammopathy of uncertain significance to myeloma. However, the level of the paraprotein (>15 g/litre), isotype of the monoclonal protein (non-IgG

Table 3. Diagnostic criteria for monoclonal gammopathy of uncertain significance, asymptomatic myeloma and symptomatic myeloma

Monoclonal gammopathy of uncertain significance	Asymptomatic myeloma	Symptomatic myeloma
Paraprotein in serum < 30 g/litre, clonal plasma cells <10% bone marrow	Paraprotein in serum > 30 g/litre and/or bone marrow clonal plasma cells > 10%	Paraprotein in serum and/or urine (no specific level required for diagnosis), bone marrow (clonal) plasma cells
No myeloma-related organ or tissue impairment bone lesions or symptoms)	No myeloma-related organ or tissue impairment (including bone lesions or symptoms)	Myeloma-related organ or tissue impairment (including (including bone lesions or symptoms)
No evidence of other B-cell lymphoproliferative disorder or light chain-associated amyloidosis or other light chain, heavy chain or Ig-associated tissue damage		

Adapted from UK Myeloma Forum Nordic Myeloma Study Group Guidelines (Bird et al, 2009)

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isotype) and abnormal serum free light chain ratio are helpful in identifying patients at a higher risk of progression. For those patients with all factors abnormal, the risk of progression is 58% at 20 years, whereas patients with no abnormal factors are at low risk at 5% at 20 years follow up (Kyle et al, 2002, 2010). In practice, when considering competing causes of death within what is essentially an elderly population of patients, the patient is at greater risk of death from other causes rather than dying ultimately from myeloma.

With this in mind, the current recommendations are that patients with monoclonal gammopathy of uncertain significance are initially reviewed in haematology clinic every 4–6 months for the first 1–2 years and then less frequently. Follow up in primary care is entirely appropriate for most patients. Alternatively, patients can be followed up in a hospital-based nurse-led clinic. At each appointment, patients require repeat history and examination, full blood count, renal function, calcium and paraprotein quantification in serum and urine. Patients should be re-referred for review by a haematologist if there is a significant rise in paraprotein, development of anaemia or other cytopaenia, renal dysfunction, hypercalcaemia, new back pain, new bone pain or recurrent infections. There is currently no specific treatment for monoclonal gammopathy of uncertain significance (Berenson et al, 2010).

Asymptomatic myeloma: prognosis and management

Patients with smouldering (asymptomatic) myeloma have an excess of clonal plasma cells in the bone marrow (at least 10%), or a paraprotein level of 30 g/litre or more, without any end organ damage. Asymptomatic myeloma accounts for 15% of all new cases of myeloma. It needs to be distinguished from monoclonal gammopathy of uncertain significance because of a higher risk of progression to symptomatic myeloma (10% *vs* 1% per year for monoclonal gammopathy of uncertain significance). The risk of progression relates to the amount of paraprotein (≥30 g/litre), percentage of plasma cells in the bone marrow (≥10%), and abnormal free light chain ratio. For those patients with all factors abnormal, the risk of progression is 76% at 5 years, compared to those with one abnormal factor where the risk is 25% at 5 years (Kyle et al, 2010). Importantly the risk of progression falls with time, from 10% per year for the first 5 years, 3% per year for the following 5 years, and 1% per year thereafter.

There is no specific treatment required for asymptomatic myeloma but these patients should be followed up in haematology clinic. There are ongoing clinical trials looking at the use of novel agents in patients with early stage disease.

Myeloma: brief overview of management

It is beyond the scope of this article to cover the entirety of myeloma management. This section gives a brief overview of the salient points (Bartolegie et al, 2004; Kyle and Rajkumar, 2009; Bird et al, 2011; Moreau et al, 2013).

Myeloma makes up 1% of all cancers. It is incurable, but patients often respond well to treatment. It usually follows a relapsing/remitting pattern after treatment. It is progressive without therapy. There have been significant advances recently, with new therapies improving the quality of life and prognosis for patients diagnosed with myeloma. The prognosis is in excess of 7 years for those patients responding to initial therapy and proceeding to autologous stem cell transplantation, with a shorter life expectancy in the frail elderly patient.

Management of multiple myeloma requires input from a wide range of medical specialities including palliative care. The treatment of myeloma is broadly divided into specific treatment for myeloma itself and supportive care.

For younger patients (usually aged 65 years old and less), treatment is with induction chemotherapy (outpatient based) followed by high-dose chemotherapy with autologous stem cell rescue (autologous transplant). Older and frailer patients receive induction chemotherapy alone. All patients will inevitably relapse and are likely to respond to further chemotherapy (and also at subsequent relapse). Chemotherapy involves the use of steroids, proteasome inhibitors (bortezomib or carfilzomib), immune modulatory agents (thalidomide, lenalidomide or pomalidomide) often given in combination with alkylator drugs (such as melphalan or cyclophosphamide).

Supportive care includes the management of pain, hypercalcaemia, renal impairment, anaemia, infection and hyperviscosity. Bisphosphonates have an important place in the treatment and prevention of

Table 4. Myeloma-related organ or tissue impairment

Increased calcium levels	Corrected serum calcium >0.25 mmol/litre above the upper limit of normal or >2.75 mmol/litre
Renal insufficiency	Attributable to myeloma
Anaemia	Haemoglobin 20 g/litre below the lower limit of normal or haemoglobin <100 g/litre
Bone lesions	Lytic lesions or osteoporosis with compression fractures (magnetic resonance imaging or computed tomography may clarify)
Other	Symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (> two episodes in 12 months)

Adapted from UK Myeloma Forum Nordic Myeloma Study Group Guidelines (Bird et al, 2009)

TOP TIPS

- Myeloma can present in many different ways so it is frequently appropriate to test for the presence of paraproteinaemia.
- It is essential to request serum protein electrophoresis and urinary Bence Jones protein. These are always supplemented by full blood count, renal function, corrected calcium and full skeletal survey.
- General physicians should be aware that myeloma can present acutely with bony fractures, renal failure, hypercalcaemia, spinal cord compression, sepsis and hyperviscosity. These conditions require emergency management.

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hypercalcaemia. Anaemia tends to improve with the treatment of the underlying myeloma but transfusion of packed red cells may also be required. The risk of infection is increased in myeloma as a result of the paraproteinaemia, immune paresis and the myeloma treatments themselves.

Management of other causes of paraproteinaemia

Patients with lymphoplasmacytic lymphoma who are asymptomatic do not require treatment. Indications for treatment are hyperviscosity, anaemia or other cytopaenia, lymphadenopathy or systemic symptoms such as sweats. Patients are treated with chemotherapy both initially and at relapse.

Patients with AL amyloid present with symptoms related to deposition of the paraprotein in affected organs. Classic sites include cardiac, renal, peripheral and autonomic nerves, and the gastrointestinal tract. Treatment of the underlying plasma cell clone is as for myeloma, although patients may not tolerate more aggressive chemotherapy.

Rarely, the circulating paraprotein can cause type 1 cryoglobulinaemia. Treatment is of the underlying plasma cell clone.

Conclusions

Paraproteinaemia is a common finding in general medical and elderly care patients and can be secondary to a wide range of clinical conditions, most frequently monoclonal gammopathy of uncertain significance and multiple myeloma. It is essential to differentiate these two conditions as monoclonal gammopathy of uncertain significance is an asymptomatic condition requiring monitoring only whereas myeloma is a haematological malignancy requiring supportive care and chemotherapy. This article summarizes how to test for paraproteinaemia, when to request the test, and reviews the differences between monoclonal gammopathy of uncertain significance and myeloma. BJHM

Conflict of interest: none.

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KEY POINTS

- A paraprotein arises from the abnormal clonal proliferation of mature B cells.
- The incidence of paraproteinaemia is 3.2% in those over the age of 50 years and becomes increasingly more common in advancing age.
- The most common causes are monoclonal gammopathy of uncertain significance, myeloma and lymphoplasmacytic lymphoma.
- Although monoclonal gammopathy of uncertain significance is a pre-malignant condition, it has a risk of 1% per year of progression to myeloma.
- The variables that differentiate between monoclonal gammopathy of uncertain significance and myeloma are: level of paraproteinaemia, percentage of bone marrow plasma cells, presence or absence of related organ or tissue impairment.
- Monoclonal gammopathy of uncertain significance and asymptomatic myeloma require lifelong follow-up in haematology clinic or primary care.
- The management of multiple myeloma requires input from the multidisciplinary team and consists of supportive and specific management, frequently with chemotherapy and/or radiotherapy.

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