Myeloma and MGUS

Aikaterini Panopoulou

Matthew J Streetly

Abstract

Plasma cell disorders result from a clonal proliferation of bone marrow plasma cells and range from relatively benign monoclonal gammopathy of undetermined significance (MGUS) to malignant myeloma. Serum or urine monoclonal protein is usually detectable. MGUS is asymptomatic but can progress to myeloma or lymphoma. Myeloma is generally a disease of elderly individuals and presents with variable problems including anaemia, bone pain, fractures, spinal cord compression, renal failure, hypercalcaemia, recurrent infections and hyperviscosity. Diagnosis is based on bone marrow examination, and prognosis is influenced by specific genetic abnormalities. Treatment is required for the development or imminent risk of development of myeloma-related organ or tissue impairment, and when any myeloma-defining biomarker is identified. Myeloma is incurable, and treatment combines anti-myeloma chemotherapy and supportive therapy. Younger, medically fit patients are treated with intensive regimens combining chemotherapy with autologous stem cell transplant, whereas older patients with medical co-morbidities and poorer performance status are given chemotherapy alone. It has a responding and relapsing course with eventual development of drug resistance. However, the availability of newer drugs, such as bortezomib, lenalidomide, panobinostat and pomalidomide, along with improvements in supportive care, such as regular bisphosphonates, is leading to improved disease-free and overall survival.

Keywords Bisphosphonates; electrophoresis; monoclonal gammopathy of undetermined significance; myeloma; paraprotein

Key points

- Myeloma is preceded in most patients by the premalignant state of monoclonal gammopathy of undetermined significance
- Detection of genetic abnormalities by fluorescent *in situ* hybridization has prognostic value (e.g. t(4; 14) and del(17p) are predictors of poor risk)
- The new International Myeloma Working Group criteria incorporate pathological, biochemical and radiological biomarkers to identify and offer early treatment to a group of asymptomatic but ultra-high-risk patients who would previously have been monitored
- Modern imaging techniques with MRI and PET-CT have antiquated conventional radiography in the detection of myeloma bone disease because of their high sensitivity, growing availability and contribution to offer of early treatment in patients with bone lesions
- New drug combinations and novel therapies have led to improved overall response rates, longer duration of disease control and improved overall survival, promising a change in the natural history of this incurable disease. Further promising agents including targeted therapies such as monoclonal antibodies (e.g. the anti CD-38 monoclonal antibodies daratumumab) and histone deacetylase inhibitors (e.g. panobinostat) and next-generation improvements on existing drugs are subject to current research in ongoing clinical trials

Introduction

Myeloma is an incurable yet treatable malignancy characterized by the clonal proliferation of bone marrow plasma cells that can cause bone lesions, anaemia, renal failure and recurrent infections. It is usually (but not exclusively) associated with a detectable serum or urinary monoclonal protein.

Plasma cells are a key component of the immune system and in particular of immunological memory (humoral immunity). They develop as a result of differentiation and maturation of B cells, and represent the most terminally differentiated cells of this lineage. In healthy individuals, their role is to produce immunoglobulins (Igs; antibodies) that are specific for a single encountered antigen in the blood, lymph nodes or tissues.

Aikaterini Panopoulou ***MB BS MRCP*** *is a Specialist Registrar in Haematology at Guy's and St Thomas' Hospital, London, UK. Competing interests: none declared.*

Matthew J Streetly ***BM BS PhD MRCP FRCPath*** *is a Consultant Haematologist at Guy's and St Thomas' Hospital, London, UK. His research interests include treatment of myeloma with novel therapies and the bone marrow microenvironment in myeloma. Competing interests: none declared.*

Humoral immunity provides protection against an enormous diversity of antigens, resulting in a wide polyclonal range of Igs. In contrast, a malignant clonal proliferation of plasma cells produces excessive amounts of identical Igs termed monoclonal proteins or paraproteins.

Detection and association of paraproteins

Paraproteins are detected by serum or urine protein electrophoresis and identified by immunofixation (Figure 1). Most serum paraproteins comprise a heavy and light chain, whereas urinary paraproteins (Bence Jones protein) usually have only light chains as the glomerulus limits the passage of larger proteins. The serum free light chain (SFLC) assay employs antibody detection of free κ and λ light chains in the serum and has largely superseded urinary electrophoresis.

Although myeloma and monoclonal gammopathy of undetermined significance (MGUS) are the most common associations with paraproteins, they can also be detected in AL amyloidosis, solitary plasmacytoma, Waldenström's macroglobulinaemia, various lymphomas and rare syndromes such as POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin changes).[1] It is suggested that all patients

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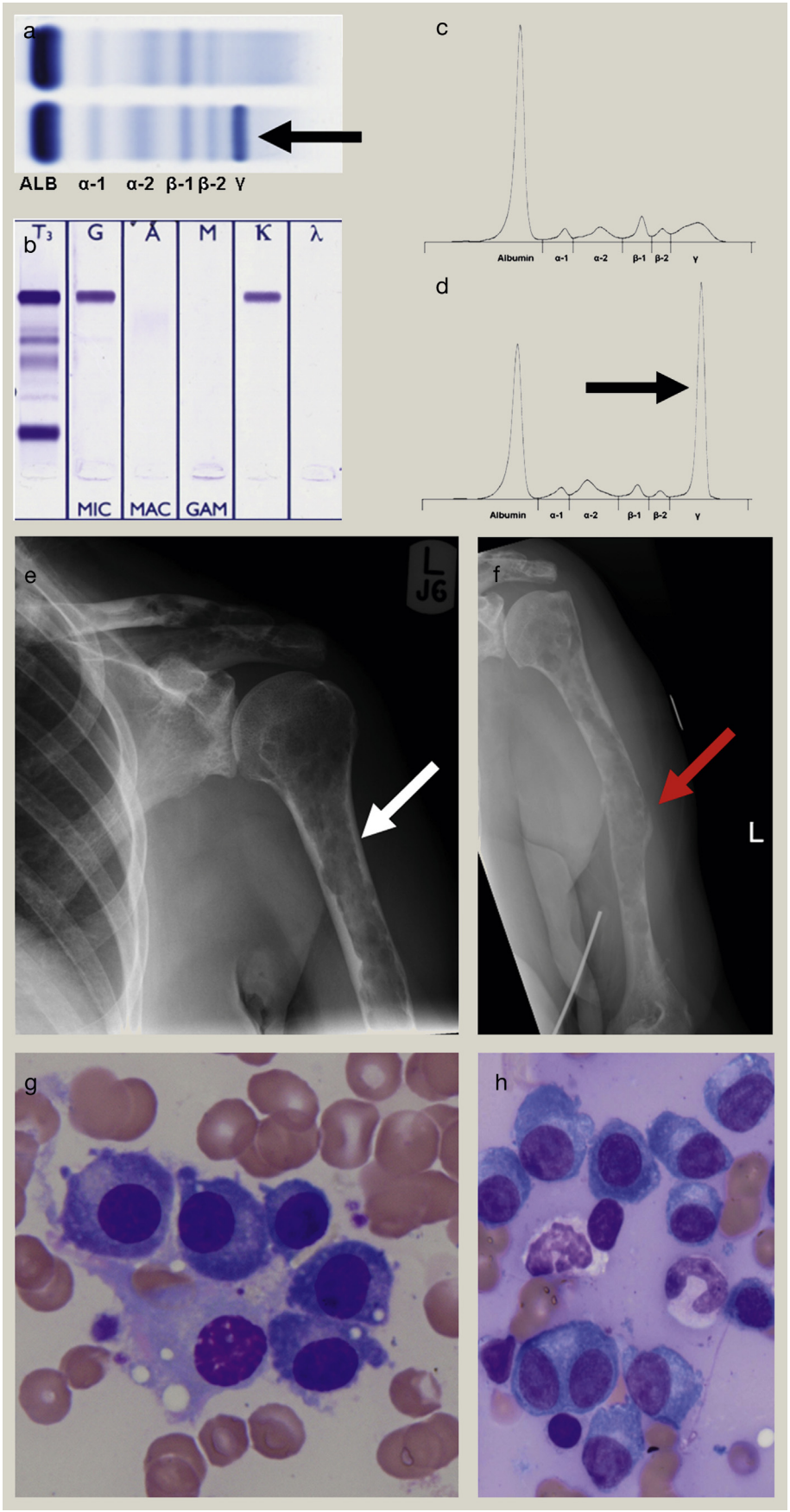

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