ATUL B. MEHTA • KEITH GOMEZ

ILLUSTRATED CLINICAL CASES

Clinical Haematology

SECOND EDITION

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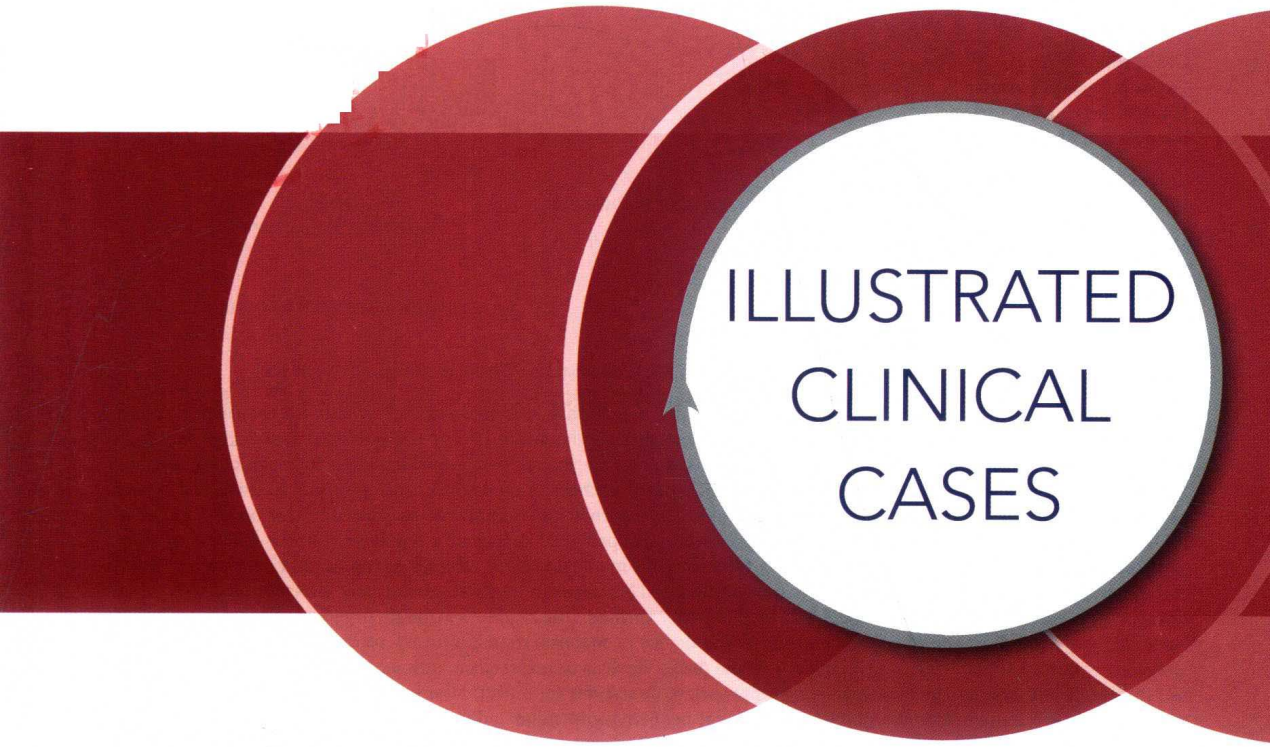

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FOREWORD

In his foreword to the first edition of *Clinical Haematology*, Professor Luccio Luzzatto identified the interest in a combined laboratory and clinical specialty as one of the key features that attract young clinicians to haematology. This continues to be the case and it is this interest in interpreting laboratory data relevant to a clinical presentation that haematologists find compelling. This attraction is also evident in clinical laboratory scientists who are likewise drawn to the clinical interface in their roles in data interpretation and quality assurance.

Atul Mehta and Keith Gomez have produced a book which absolutely captures the essence of clinical haematology, using a range of clinical histories illustrated with numerous different forms of diagnostic material, from clinical photographs to photomicrographs of blood and bone marrow, CT, MRI, and PET scans, haemoglobin electrophoresis and HPLC, FACS plots, and platelet aggregation, to mention a few. The book takes us through general and malignant haematology to haemostasis and thrombosis, and finishes with several scenarios related to quality control and quality assurance.

What I really like about this book is the way the cases are presented, such that the reader ends up working through them in a way that replicates the process in real life. I think this book will appeal to trainees in medicine and especially trainees in haematology. There is little doubt that those preparing for exit exams in haematology such as the membership of the Royal College of Pathologists UK, and similar, will find this book helpful. In addition, the book will appeal to clinical scientists, established consultants and specialty grade doctors practising haematology.

I would like to congratulate both authors on their book and hope that their readers enjoy working through the cases as much as I did.

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With a Foreword by Dr. Henry Watson
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LIST OF ABBREVIATIONS

ABC	activated B cell
ACD	anaemia of chronic disease
AIHA	autoimmune haemolytic anaemia
ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukemia
ANF	anti-nuclear factor
APML	acute promyelocytic leukemia
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATRA	all-trans retinoic acid
CALR	calreticulin
CBF	core binding factor
CLL	chronic lymphocytic leukaemia
CMV	cytomegalovirus
CNS	central nervous system
CT	computed tomography
DAT	direct anti-globulin
DVT	deep vein thrombosis
EBV	Epstein–Barr virus
EPO	erythropoietin
ERCP	endoscopic retrograde cholangiopancreatography
ERT	enzyme replacement therapy
ESR	erythrocyte sedimentation rate
FAB	French–American–British
FDP	fibrin degradation product
FFP	fresh-frozen plasma
FISH	fluorescent in situ hybridization
FLAER	fluorescently labeled aerolysin
G6PD	glucose-6-phosphate dehydrogenase
GGL	chronic granulocytic leukaemia
GGT	Gamma-glutamyl transferase
GI	gastrointestinal
GP	general practitioner
GVHD	graft versus host disease
Hb	Haemoglobin
HL	Hodgkin's lymphoma
HLA	human leukocyte antigen
HLH	haemophagocytic lymphohistiocytosis
HMWM	high-molecular weight multimers
HPA	human platelet antigen
HPLC	high-performance liquid chromatography
INR	international normalised ratio
IPS	International Prognostic System
ITP	immune thrombocytopenia
IV	intravenous
IVIG	intravenous immunoglobulin
IVU	intravenous urogram
LDH	lactate dehydrogenase
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MRI	magnetic resonance imaging
NADPH	nicotinamide adenine dinucleotide phosphate
NAP	neutrophil alkaline phosphatase
NHL	non-Hodgkin's lymphoma
PA	Pernicious anaemia
PA	posteroanterior
PCV	packed cell volume
PET	positron emission tomography
PNH	paroxysmal nocturnal haemoglobinuria
PT	prothrombin time
RBC	red blood cells
RE	reticuloendothelial
RIPA	ristocetin-induced platelet aggregation
SRT	substrate reduction therapy
TK	tyrosine kinase
TNF	tumour necrosis factor
TSH	thyroid-stimulating hormone
TTP	thrombotic thrombocytopenic purpura
VWF	von Willebrand factor
WBC	white blood cells
WHO	World Health Organization

CONTENTS

GENERAL AND MALIGNANT HAEMATOLOGY

CASE 1

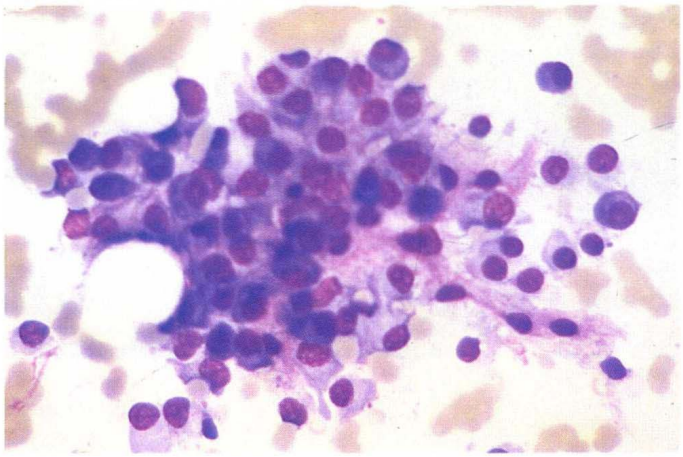
QUESTIONS

A 76-year-old man has a 2-week history of abdominal pain, polyuria and nocturia. He has also noticed a skin nodule which is increasing in size. Investigations show

Haemoglobin (Hb)	71 g/L
White blood cells (WBC)	4.6×10^9/L
Platelets	112×10^9/L
Urea	46 mmol/L
Creatinine	905 mmol/L
Ca^{2+}	3.60 mmol/L (N 2.1–2.6 mmol/L)
Albumin	26 g/L (N 35–42 g/L)
Total protein	120 g/L (N 65–80 g/L)
Alkaline phosphatase	143 U/L (N 30–130 U/L)
Uric acid	0.48 mmol/L (N 0.3–0.4 mmol/L)

Q1.i Comment on the above results.

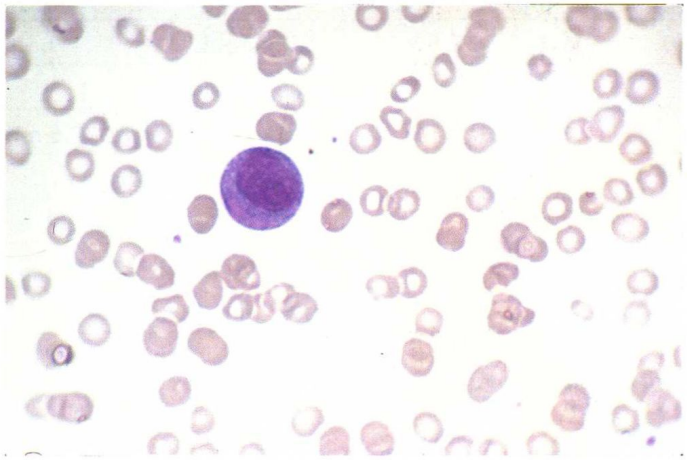
Q1.ii Comment on the bone marrow aspirate.



Case 1: ANSWERS

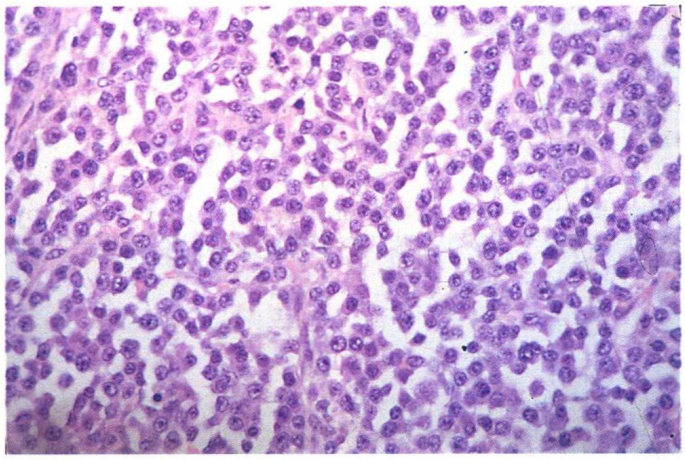
A1.i The results indicate anaemia and thrombocytopenia with marked renal failure. Hypercalcaemia with normal alkaline phosphatase suggests primary bone marrow malignancy. The raised total protein suggests myeloma.

A1.ii The bone marrow is infiltrated by plasma cells, confirming myeloma. Plasma cell leukaemia is an aggressive form of myeloma characterised by large numbers of circulating plasma cells.

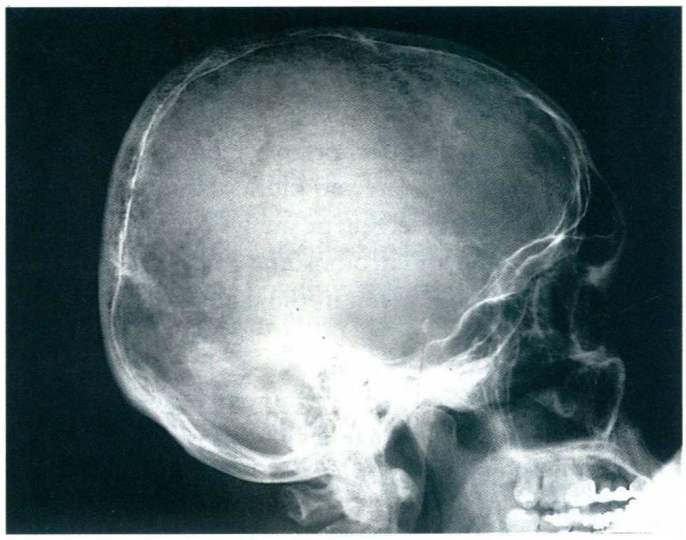


Case 1: QUESTIONS (Continued)

Q1.iii Comment on the aspirate of this patient's skin nodule.



Q1.iv Comment on the skull x-ray.



Q1.v What is the diagnosis?

Q1.vi How should he be treated?

Case 1: ANSWERS (Continued)

A1.iii The skin deposit is also due to myeloma infiltration.

A1.iv The skull x-ray shows multiple lytic lesions, a characteristic finding in myeloma.

A1.v Myeloma.

A1.vi The hypercalcaemia and renal failure require urgent therapy with rehydration to promote diuresis. An intravenous urogram (IVU) should not be done as the patient should not be dehydrated. However, abdominal ultrasound scan to exclude renal obstruction is valuable in acute renal failure.

Baseline tests should include paraprotein quantification in serum and urine (Bence Jones protein), skeletal survey, beta-2 microglobulin and C-reactive protein. Other baseline tests should include a coagulation profile, culture of mid-stream urine and assessment of antibodies to hepatitis A, B and C. Serum-free light chains should be estimated as they are elaborated by the tumour cells and are often the principal cause of the renal toxicity. A renal biopsy should be considered, and the nephrologist will wish to undertake a range of tests to exclude other causes of acute renal impairment. A complete cardiac assessment including echocardiography is important, and the presence of amyloid deposition, for example, in heart and kidneys should be considered. Baseline assessment should also include genetic analysis of the cells by fluorescent in situ hybridization (FISH) and/or chromosome analysis. The International Staging System (ISS) for myeloma is given in the table.

Molecular changes in myeloma

1. Translocations involving immunoglobulin heavy chain (Igh) locus, e.g. t(11;14) (translocation of *CCND1*), t(4;14) (dysregulation of fibroblast growth Factor III and multiple myeloma SET [*MMSET*] domain)
2. Copy number alterations, e.g. hyperdiploidy, deletion 13, gains of 1q, trisomies, 17p deletion
3. Mutation – e.g. in ERK pathway
4. Methylation modification
5. Late events as markers of clonal progression, e.g. *RAS* activation, *MYC* dysregulation

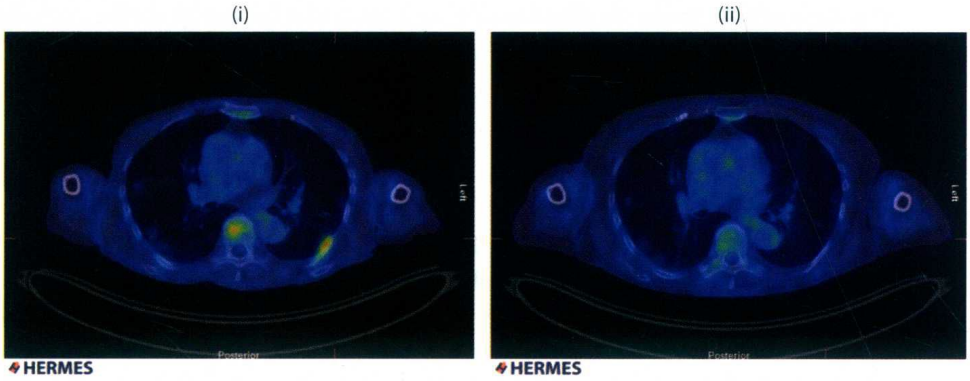
ERK, extracellular signal-related kinases.

International Staging System

Stage I	Beta-2 microglobulin <5.3 mg/dL, albumin >35 mg/dL
Stage II	Remainder
Stage III	Beta-2 microglobulin >5.5 mg/dL

Case 1: ANSWERS (Continued)

Imaging techniques are important for detection of skeletal and neurologic involvement. There is increasing interest in the use of fluorodeoxyglucose (FDG)–positron emission tomography (PET) scans for detection of active myeloma deposits (as opposed to old and possibly healed skeletal deposits) and treatment can be targeted towards resolution of observed abnormalities. Thus, a set of pre- and post-treatment images are recorded as shown in the figure.



Fluorodeoxyglucose (FDG)–positron emission tomography (PET) scan in myeloma to show active bone disease. (i) Pre-treatment. (ii) Post-treatment.

The patient should receive allopurinol (at a reduced dose of 100 mg/day because of his renal failure) followed by steroid therapy for hypercalcaemia. If the calcium remains elevated, consider bisphosphonates, for example, zoledronic acid or pamidronate, given by intravenous (IV) infusion, dose adjusted for renal impairment. The renal failure may warrant institution of dialysis.

Chemotherapy should be commenced once he is stabilised. Bortezomib is a proteosome inhibitor which is administered subcutaneously alongside dexamethazone. Addition of an anthracycline drug, for example, Adriamycin should be considered; it can be given as an infusional regime with the bortezomib and dexamethazone. There is evidence that intensive early treatment aimed at reducing the tumour burden and the serum level of free light chains may help to restore renal function. Cyclophosphamide may be added as a weekly bolus; it is preferred in renal failure, as it is metabolised by the liver. Thalidomide is an immunomodulatory agent which also has direct anti-myeloma effects; side effects include drowsiness, constipation, neuropathy and a critical need to avoid pregnancy (self or partner). A stable ('plateau') phase of the disease is typically achieved after four to six cycles of chemotherapy. Long-term bisphosphonate therapy (e.g. sodium clodronate) may slow progress of skeletal disease in myeloma. The typical course of myeloma is that patients relapse but will respond to reinstitution of chemotherapy. Thalidomide derivatives include lenalidomide, which has an

increasing role as a first-line agent as it has greater activity than thalidomide and less neurotoxicity and it is also less likely to provoke thrombosis. Pomalidomide is a derivative that has activity in subjects who are resistant to lenalidomide. Other options include melphalan and (intermittent oral) prednisolone (+/− thalidomide); further courses of bortezomib or its newer derivatives (e.g. carfilzomib, a newly licensed proteosome inhibitor with less neurotoxicity than bortezomib; or ixazomib, which can be given orally) with dexamethazone. Bendamustine and dexamethazone may be considered. Older regimes which may have a role in relapsed patients include vincristine, adriamycin, both by IV infusion, and dexamethasone (VAD), and the combination of idarubicin and dexamethazone.

Younger patients (those under 65) with myeloma may benefit from intensive therapy, including autologous transplant of peripheral blood stem cells. Patients under 50 who have a human leukocyte antigen (HLA)-matching sibling may be considered for allogeneic haemopoietic stem cell transplantation, though this has a greater toxicity and lesser efficacy than in acute leukaemia and relapsed lymphoma. A monoclonal antibody with specificity against CD38 has been recently licensed and has activity both as a single agent and in combination with pomalidomide.

CASE 2

QUESTIONS

A 42-year-old woman gives a 2–3 month history of abdominal pain, diarrhoea and rectal bleeding. She passes blood-stained motions four to six times each day. She has also developed progressive tiredness and loss of appetite. On examination she is pale. There is no lymphadenopathy. She has mild generalised abdominal tenderness, but there is no organomegaly. Her blood count shows

Haemoglobin (Hb)	84 g/L
Mean corpuscular volume (MCV)	110 fL
White blood cells (WBC)	3.1×10^9/L
Platelets	80×10^9/L

Biochemistry is normal, but the erythrocyte sedimentation rate (ESR) is raised at 86 mm/h.

Q2.i What diagnosis is suggested by the barium meal and follow-through (Figure 2a)?

Q2.ii What abnormalities are seen in her bone marrow aspirate (Figures 2b through 2d)? What is the diagnosis?

Q2.iii What further investigations would you perform?