Case Number 12
An Unusual Case of Multiple Myeloma

Daniel Farrugia and Julian Delicata
Reviewed by Dr. D .J. Camilleri

Case summary:

The case concerns the unusual presentation of a non-secretory multiple myeloma with diarrhoea secondary to large bowel infiltration.

In December 2009, a 74-year-old lady presented to hospital and complained of a two year history of intermittent diarrhoea which had been worsening over a three month period. She also had sustained a deep vein thrombosis and was investigated for pulmonary embolism. Routine blood investigations showed a raised ESR & CRP and a normochromic normocytic anaemia. Urea and electrolytes, liver function tests, calcium, phosphate and albumin where all normal, creatinine was elevated. Serum protein electrophoresis was normal at presentation. Chest X-ray revealed lytic rib and vertebral lesions which were followed by CT scan and MRI. Colonic biopsy revealed a plasma cell infiltration and rib trucut biopsy revealed plasmacytoma. Bone marrow biopsy confirmed Multiple Myeloma.

Presenting complaint:

December 2009: 74-year-old woman presented with a prolonged history of repeated watery stool motions becoming frequent - up to 12 times a day. She reported no signs of bowel cramping and denied any bleeding PR. There were no other associated features such as hot flushes, nausea and vomiting or dyspnoea. No weight loss. She had low grade pyrexia on admittance.

History of presenting complaint:

The patient reported a prolonged history of watery diarrhoea of up to two years, which she controlled using Imodium. The frequency had become progressively worse over the past several months up to 12 times a day necessitating hospital admission.

Past medical history and surgical history:

Past medical history:

- Hypertension
- Possible chronic renal insufficiency secondary to hypertension
- Hypothyroidism
- Osteoarthritis
- Hypercholesterolaemia

Past surgical history:

- Total abdominal hysterectomy-bilateral salpingo-oopherectomy
- Bladder surgery
- Lower segment Caesarean Section
- Cataract extraction

Systemic inquiry

- Cardiorespiratory System: nothing of note.
- Genitourinary System: nothing of note.
- Central Nervous System: nothing of note.
- Endocrine System: nothing of note; Hypothyroidism well controlled on Levothyroxine.
- Musculoskeletal System: suffers from Osteoarthritis for which she takes NSAIDS intermittently.

Drug history:

Drug	Dosage	Frequency	Type	Reason
Perindopril	4mg	BD	ACE inhibitor	Used as an anti-hypertensive
Catafast	Not Specified	Intermittently	NSAID	Pain relief for Osteoarthritis
Nortrilen	10mg	Nocte	Tricyclic Anti-depressant; Nortriptyline	Anti-depressant
Lexamil	1.5mg	Nocte	SSRI	Anti-depressant
Zopiclone	3.5mg	Nocte	Non-benzodiazepine	Hypnotic
Salazopyrine	500mg	TDS	Aminosalicylate	Osteoarthritis
Folic Acid	5mg	Daily	Vitamin B9	Vitamin supplement due to Salazopyrine treatment
Cholestyramine	4g	BD	Bile Acid Sequestrant	Hypercholesterolaemia
Nexium	20mg	Daily	Proton Pump Inhibitor	Gastro-oesophageal reflux disease
Dioralyte	2 Sachets	Daily	Electrolytes	Electrolyte replenishment in view of chronic diarrhoea
Candesartan	16mg	Daily	Angiotensin Receptor Blocker	Hypertension
Imodium	2mg	Q.I.D	Opioid Agonist; Loperamide	Anti-diarrhoeal
Eltroxine	100mcg	Daily	Levothyroxine	Thyroid medication

Family history:

Nothing of note.

Social history:

Married wife with two children and owns a shop selling textiles. Housewife.

Current therapy:

Irrelevant to the case. All treatment listed in Therapy section later on.

Discussion of results of general and specific examinations:

General examination was unremarkable and revealed nothing useful apart from low-grade pyrexia. Inflammatory Bowel Disease was excluded via colonoscopy and biopsy and histology and the latter

revealed plasma cell infiltration of the colon. Faecal microscopy and culture ruled out parasitic and bacterial causes. Coeliac serology was negative as was 24 hr Urinary 5-HydroxyIndoleAcetic acid testing making both Coeliac disease and Carcinoid syndrome respectively, an unlikely cause of diarrhoea.

Radiology was requested in view of DVT developed one month after presentation. Chest X-ray revealed an incidental 9th right rib lesion, confirmed as a plasmacytoma on trucut biopsy. T2 and T6 lytic lesions were found on CT scan. Serum protein electrophoresis revealed no monoclonal gammopathy, but serum free light chain ratio was elevated at 5.5, as was β2-Microglobulin at 3.8mg/L bone marrow biopsy confirmed Multiple Myeloma diagnosis. Normochromic normocytic anaemia; raised ESR; CRP and creatinine were all supplementary to the diagnosis, but the latter should be considered in light of hypertensive disease and possible chronic renal failure. The disease was staged at II-IIIA by Durie Salmon Staging system using results obtained, and at Stage I by the International Staging System.

Differential Diagnosis:

- Inflammatory Bowel Disease
- Parasitic/ Bacterial Gastroenteritis
- Coeliac Disease
- Carcinoid Tumour

Diagnostic Procedures:

The diagnostic procedures performed in December 2009 will be listed here. Divided into five parts:
1. Blood investigations
2. Microbiology
3. Radiology
4. Instrumental investigations
5. More specific tests

Laboratory Investigations:

Blood investigations:

Test: Full blood count
Justification for test: To check for anaemia for possible malabsorption; chronic disease; to check for infection.
Result: Haemoglobin 9.9g/dL, MCV: 87fL.
Conclusion: Normocytic Normochromic Anaemia.

Test: ESR & CRP
Justification for test: To check for an inflammatory process.
Result: ESR was 80mm/hr; CRP was 30mg/L
Conclusion: Inflammatory process is present.

Test: Urea and Electrolytes; Corrected Calcium Levels:
Justification for test: To check for electrolyte abnormalities in view of chronic diarrhoea.
Results: Urea: 5.7mmol/l; Potassium: 4.3mmol/l; Sodium: 137mmol/l
Creatinine: 135umol/L;
Corrected Calcium: 2.6mmol/L
Conclusion: Creatinine is elevated. Calcium is within normal range.

Test: Liver Function Tests
Justification for test: IBD associated deranged LFTs; Liver involvement in view of carcinoid syndrome-like symptoms.
Result: Within normal ranges
Conclusion: LFT's are normal; does not exclude mentioned disease.

Test: Albumin
Justification for test: Possible Protein losing enteropathies.
Result: Normal: 40g/L
Conclusion: Protein Losing Enteropathy unlikely.

Test: Thyroid Function Tests
Justification for test: Known Hypothyroidism on medication.
Result: Within normal ranges.
Conclusion: Controlled Hypothyroidism.

Microbiology

Test: Stool cultures & microscopy for bacteria; microscopy for ova; cysts for parasites.
Justification for test: Check for possible bacterial and parasitic cause for chronic diarrhoea.
Result: Negative.
Conclusion: Bacterial and parasitic causes excluded.

Radiology

Test: Chest X-ray
Justification for test: Investigation for pulmonary embolism.
Result: 9th rib lesion noted on chest X-ray.
Conclusion: Bone lesion to be biopsied for histology. No signs of PE seen on X-ray.

Test: CT Pulmonary Angiogram
Justification for test: Investigation for pulmonary embolism in view of DVT sustained.
Result: Pulmonary embolism present.
Conclusion: Pulmonary embolism confirmed.

Test: CT chest/abdomen/pelvis
Justification for test: To check for any other bone lesions in view of CXR findings.
Result: Lesion in 9th rib confirmed. Two lytic lesions in T2 & T6 vertebrae were identified.
Conclusion: Rib lesion to be biopsied for histology.

Test: MRI spine
Justification for test: Check for any lesions that could not be identified on CT.
Result: No other significant findings.
Conclusion: No significant findings, other than those identified on CT already.

Instrumental Investigations

Test: Colonoscopy & colonic biopsies
Justification for test: To investigate the presence of Inflammatory Bowel Disease (IBD) and other neoplastic pathology.
Result: Plasma cell infiltration on histology, normal mucosa.
Conclusion: IBD unlikely.

More Specific Tests

Test: 24 hour urine collection for HIAA (5-Hydroxyindoleacetic acid)
Justification for test: Carcinoid tumour.
Result: Negative.
Conclusion: Carcinoid tumour unlikely.

Test: Coeliac serology
Justification for test: In view of symptoms described.
Result: Negative.
Conclusion: Coeliac disease unlikely.

Test: Right 9th Rib lesion Trucut biopsy
Justification for test: In view of CT scan findings.
Result: Plasmacytoma on histological analysis.
Conclusion: Multiple lesions indicate Plasmacytomas.

Test: Serum protein electrophoresis (SPE)
Justification for test: To investigate findings suggestive of multiple myeloma.
Result: No monoclonal spike of note in gamma position.
Conclusion: No monoclonal gammopathy present.

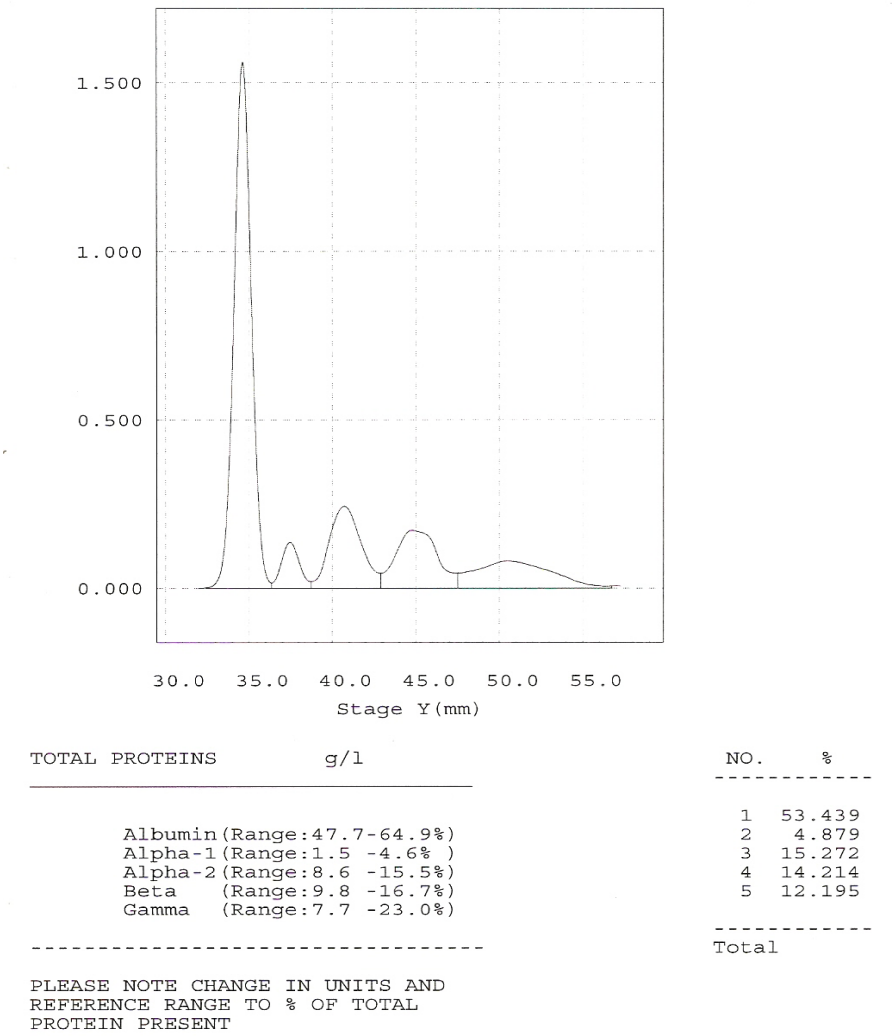

Figure 1: This graph shows the first Serum Protein Electrophoresis (SPE) taken and shows no significant spike in gamma position (the latter being the 5th and last curve of the graph).

Subsequent SPEs taken during therapy show a Hypogammaglobulinaemia as normal immunoglobulin levels decrease secondary to chemotherapeutic regimen.

Test: Serum Free Light Chain Ratio (SFLC)
Justification for test: In view of biopsy findings and normal SPE result.
Result: 5.5
Conclusion: The SFLC ratio is deranged indicating Multiple Myeloma.

Test: Beta-2 Microglobulin
Justification for test: In view of biopsy findings. Useful prognosticator.
Result: 3.8mg/L
Conclusion: Elevated. Normally elevated in Plasma Cell Dyscrasias and Lymphoproliferative Disorders.

Test: Bone Marrow Biopsy
Justification for test: In view of Plasmacytoma.
Result: Plasma cell infiltration of 20%.
Conclusion: Multiple Myeloma confirmed.

Therapy

Drugs:

Cyclophosphamide Thalidomide Dexamethasone (CTD) regimen was initiated for an indefinite period of time as treatment to Multiple Myeloma as according to CDT protocol.

Drug	Dosage	Frequency	Type	Reason
Cyclophosphamide	500mg	Once Weekly	Alkylating Agent	Multiple Myeloma
Dexamethasone	20mg	Daily	Glucocorticoid	Multiple Myeloma
Thalidomide	50mg	Nocte	Immunomodulatory Drug	Multiple Myeloma
Allopurinol	300mg	Daily	Xanthine Oxidase Inhibitor	Hyperuricaemia prophylaxis for MM Chemotherapy
Septrin	960mg	Daily	Co-trimoxazole; Antibacterial	Antibiotic Prophylaxis In view of CDT regimen.
Fluconazole	50mg	Daily	Triazole Antifungal	Antifungal Prophylaxis In view of CDT regimen
Enoxaparin	100U	Daily	Low Molecular Weight Heparin	Anticoagulation therapy due to recent history of DVT and also is advised with Thalidomide and Lenalidomide therapy. No international consensus exists as to choice of anticoagulant.
Zometa	4mg	4 weekly	Zoledronate; Bisphosphonate	Osteoporosis and Hypercalcaemia Secondary to Multiple Myeloma

The patient was reviewed monthly by haematologist. Bone marrow biopsy showed Morphological Remission by 4th cycle of chemotherapy with <5% plasma infiltration. Colonic biopsy and CT scan done after 8th cycle showed regression of older lesions and no plasma cell infiltration at colonic biopsies. MRI showed no other new bony lesions.

Diagnosis:

Multiple Myeloma is a disease of uncontrolled plasma cell proliferation in the bone marrow accounting for 1% of all malignant disease and is incurable except in cases where allogeneic stem cell transplant is possible.[1, 2,3]

It peaks in incidence at the seventh decade, shows a slight predilection for male gender and increased prevalence in people of African ethnicity.[3,12,]

The disease forms part of a spectrum of disorders characterised by a Monoclonal Gammopathy (MG) which are classified according to strict criteria for distinction.[3,11]

Table 1. The following table considers criteria for classification of Myeloma related Monoclonal Gammopathies only: (adapted from reference[11])

Standard name	New name	Definition
MGUS (Monoclonal gammopathy of undetermined significance)	MGUS (Monoclonal gammopathy)	• M-protein <30g/L • Bone marrow plasma cells <10% • No "CRAB"* • No B-cell lymphoproliferative disorder
Smouldering or indolent myeloma	Asymptomatic myeloma	• M-protein ≥30 g/L and/or • Bone marrow plasma cells ≥10% • No "CRAB"*
Myeloma	Symptomatic myeloma	• M-protein in serum or urine • BM (clonal) plasma cells or plasmacytoma • "CRAB"*

*"CRAB" is organ dysfunction characterised by any one of:

C - calcium elevation (>2.75 mmol/L)
R - renal dysfunction (creatinine >173 μmol/L)
A - anaemia (haemoglobin <100 g/L)
B - bone disease (lytic lesions or osteoporosis with compression fractures)
Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months)

The monoclonal spike, when present, is usually of IgG in 60% of cases of MM.[3] The exact causes are still undefined. However, a set of genetic abnormalities such as Hyperploidy; Chromosome 14 translocations and Chromosome 13 deletions, are common to a majority of MM cases. These confer a different prognosis in patient groups with particular genetic abnormalities.[1,3,12]

Monoclonal Gammopathy of Uncertain Significance (MGUS) is a diagnosis present in 3% of the population over 50 years of age and has a 1% risk of MM progression per year.[1,3,12] The proportion of MGUS is much higher in ethnic Africans.[13]

Non-Secretory Multiple Myelomas as this case, constitute 3% of all cases and are characterised by absence or undetectable levels of monoclonal protein in serum by Serum Protein Electrophoresis (SPE) or Immunofixation.[4,11] In such cases Serum Free Light Chain Ratio (SFLC) is a more sensitive alternative to detect any change in the Free Light Chain Ratios of κ:λ which are typically 0.26-1.65.[3,5,7]

Hence in view of the absent monoclonal spike in SPE, SFLC ratio was evaluated and found to be deranged (5.5). The deranged ratio shows altered light chain production by aberrant plasma cells causing high κ

light chain levels in this case[3]. Non-Secretory Multiple Myelomas can be theoretically divided into a "Producer" type in which plasma cells produce immunoglobulin but are unable to secrete it; the "Non-Producer" type does not produce immunoglobulin[6].

There are two possible scenarios in Multiple Myeloma involvement of the bowel, the first is plasmacytoma that is extramedullary which is extremely rare, the second is by plasma cell infiltration of the GI tract which in itself is also rare and usually involves the stomach and small intestine. Very rarely large bowel can be involved as in this case, causing the unusual presentation of diarrhoea prompting in this case colonoscopic examination which was unremarkable except on biopsy and histology[8,9].

This case of multiple myeloma was confirmed on the grounds of radiological evidence of lytic bone lesions together with significant plasma cell infiltration on Bone Marrow Biopsy. The β2 microglobulin levels and albumin levels are useful for prognosis for Multiple Myeloma and are used in the International Staging System[1,10]. The elevated creatinine levels; the normochromic normocytic anaemia and high ESR and CRP are also typical features of Multiple Myeloma[3]. Durie Salmon Staging of the disease depends on Haemoglobin levels (decreased); Calcium levels (raised); Radiological findings (numbers of plasmacytomata) and quantity of Bence Jones Protein levels[10]. Creatinine levels (elevation) are also taken into account[10]. This system gives an indication of the bulk of myeloma cell mass[10].

Final treatment and follow ups:

On further review one year after colonoscopy showing remission, patient was reviewed and reported new onset low back pain radiating to the right side at the level of the 7th-8th rib.
Bone marrow biopsy from posterior iliac spine confirmed a relapsed Multiple Myeloma that showed hypercellularity and suppression of erythropoiesis. A 75% Plasma Cell Heterogeneous population with intracellular Russell Bodies was found with a proportion of plasma cells having a plasmablastic morphology. C-Reactive Protein was elevated as well. New relapse was shown to involve T9; T1; T2; T12; lumbar spine through MRI spinal imaging.

Treatment at this stage was directed at controlling pain through spinal radiotherapy and also at achieving remission through an 8 cycle plan of Velcade (Bortezomib) and Dexamethasone regimen, each cycle lasting 21 days. Zometa monthly was also added in order to control risk of fractures.
The patient sustained a pathological fracture of the right femur requiring orthopaedic intramedullary nail and subsequent rehabilitation.

Blood transfusions were given as needed according to blood haemoglobin levels. Patient also developed hypercalcaemia necessitating urgent treatment. Bone Marrow Morphological Remission after the 8th cycle of chemotherapy was achieved. Patient relapsed a second time shortly after and is due for Lenalidomide and Dexamethasone chemotherapy.

Therapy for fit patients and <65 years is chemotherapy, followed by bone marrow transplantation. This can be allogeneic or autologous stem cell transplant with the former being the ideal as it is potentially curative[4]. In this case, due to comorbidities and age, chemotherapy and maintenance regimen are advocated.

Fact Box 12:

Title: Multiple Myeloma

Short Description: This is a plasma cell disorder that characterised by abnormal proliferation and accumulation in the bone marrow. Typically it is accompanied by monoclonal protein in the serum and/or urine and consequent tissue damage such as kidney failure and pathological fractures due to bone damage.

Risk Factors:

- Age: peaks at 70
- Afro-Carribean ethnicity
- Sex: men
- Obesity
- Monoclonal Gammopathy of Uncertain Significance

Symptoms:

- Classically it presents with bone pain notably back ache
- Fatigue due to anaemia
- Recurrent infections
- Weight loss
- Abnormal bleeding tendency

Other symptoms such as:

- Anorexia
- Vomiting
- Constipation and mental disturbance follow due to hypercalcaemia symptoms
- Uncommonly amyloidosis may be symptomatic e.g. macroglossia

Signs:

- A complete blood count indicating bone marrow suppresion
- A renal profile indicating renal failure
- Lytic lesions on X-ray imaging
- Bone marrow biopsy showing bone marrow infiltration

Prevention: Patients that have Monoclonal Gammopathy of Undetermined Significance may benefit from yearly screening as they have a 1% risk of MM progression. Surveillance in patients having smouldering/asymptomatic myeloma.

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