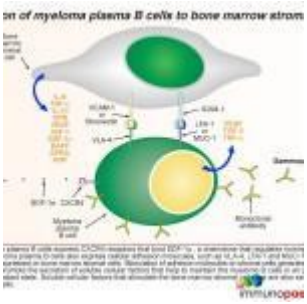
Case of enlarged hard tongue



Patient Presentation

A 59 year old male presents to the medical out patient department with a one month history of progressively increasing fatigue and backache.

Acknowledgement

This case study was kindly provided by Dr Monica Mercer, MBChB from Immunopaedia

History

For the last month the patient has been feeling exhausted for no apparent reason and due to this extreme tiredness, is

finding it difficult to work and look after himself. He comes home in the late afternoon often too tired to eat and goes straight to bed; a change from his former energetic lifestyle.

He has also been complaining of some backache which he treats with over the counter analgesics and he has been suffering from more colds and flu then usual over the last year.

He has also found that for the last 6 months there has been a decline in his ability to speak clearly. His tongue has enlarged and become firm which makes moving it for speech formation and eating solid foods difficult and at times painful.

He has had an unintentional weight loss of ± 15kg in the last 6 months.

Past medical history

Previously well, no chronic disease, no previous admissions.

Past surgical history

No history of any surgical procedures.

Family History

- Father died of a myocardial infarction at age 63 yrs with hypercholesterolaemia.
- Mother has hypertension on treatment and reports good control.
- No positive family history for any other chronic diseases including diabetes and cancer.

Social history

- Lives alone in a town house.
- Employed as an accountant.
- 30 year history of smoking.
- Significant alcohol history for 12 years, now in

recovery for the last 5 years.

Differential Diagnosis

- Anaemia
- Vitamin B12/folate deficiency
- Heart failure
- Malignancy
- Multiple myeloma
- Monoclonal gammopathy of undetermined significance (MGUS)
- Waldenstrom’s macroglobulinaemia

Examination

General

- Ill looking, pale and underweight middle-aged gentleman
- Awake and alert, able to give an accurate history
- Significant dysarthria for the last 3 months, making him difficult to understand.

Vitals

- Afebrile
- Blood pressure 100/68
- Heart rate 84
- Respiratory rate 18

General

- Mild pallor
- No lymphadenopathy
- No signs of dehydration
- No jaundice
- No oedema
- No stigmata of HIV
- Tongue red and enlarged with deep imprints from the

teeth on both sides of the tongue. Very reduced mobility; unable to protrude or lift up and very limited sideways movement.

Respiratory

- Trachea centrally located.
- Chest clear on auscultation.

Cardiovascular

- No raised JVP
- Normally placed apex beat
- S1 and S2 heart sounds present, no murmurs.
- No abnormalities detected

Abdomen

- Not distended
- Soft and non tender
- Bowel sounds present
- No abnormalities detected

Neurological

- Higher function intact, although difficult to understand
- Gait normal
- Power 5/5 globally
- Tone normal globally
- Reflexes 2/4 for both upper and lower limbs
- No abnormalities detected

Dermatological/Haematlogical

- Some small bruises on arms and legs of various ages
- No rashes
- No petaechial bleeds

Examination	Value				Normal Limits
	admission	Day 3	Day 6	Day 9	

Examination	Value				Normal Limits
WBC	5.79	6.26	6.56	6.04	(4-12 x109/L)
HB	5.4	12.8	10.9	13	(12.1-15.2 g/L)
Platelets	150	129	97	130	(140-450 x109/L)
CRP	18			14	(0-8mg/L)
Differential :					
Neutrophils		8.73			(2.00-7.5)
Monocytes		0.41			(0.18-0.80)
Lymphocytes		0.57999999999999996			(1.00-4.00)
Erythrocytes		0.03			(0.00-0.45)
Basophils		0.02			(0.00-0.20)
NA	139	140	141	146	(135-147 mmol/L)
K	6	5.3	5.4	6.2	(3.3-5.0 mmol/L)
CL	105	108	110	119	(99-103 µmol/L)
C02	18	16	18	11	(18-29 mmol/L)
Urea	23	32	37	45	(2.5-6.4 mmol/L)
Creatinine	390	291	262	316	(62-115 mmol/L)
Total protein	61	69	71		(60-80g/L)
Albumin	35	31	33		(35-50g/L)
Corrected Calcium	3.09	3.1	2.96	2.8	(2.1-2.6mmol/L)
Phosphate	2.41	1.88	1.87	1.83	(1.0-1.5 mmol/L)
Magnesium	1.1599999999999999	1.01	0.97	1.02	(0.8-1.3)
IgG		3.24			(4-10)
IgM		25.7			(0.5-2.2)
IgA		<0.33			(0.5-2.2)
B-2 microglobulin		22.3			(<3.5mg/L)
HIV Elisa	negative				
Hepatitis studies, A, B and C		All negative			
Blood Culture				Negative	
Bence Jones Protein		Positive			

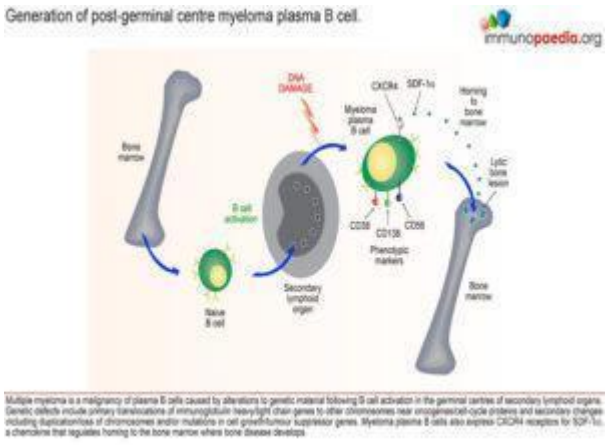
Examination	Value				Normal Limits
Bone Marrow Aspirate- phenotypic markers:					
CD38		Increased levels detected			
CD138		Increased levels detected			
Protein Electrophoresis		M band			

Discussion

This case study looks at a disease caused by the accumulation of neoplastic plasma B cells in bone marrow, which produce a monoclonal immunoglobulin protein found in the serum or urine. In serum, this is called an M protein or paraprotein. In urine, Bence-Jones proteins can be found which are specifically immunoglobulin light chains. We will examine the immunological basis of multiple myeloma, which is marked by upregulation of osteoclast activity due to overexpression of cytokines, causing lytic bone lesions. Multiple myeloma occurs in both men and women, but more common in men and manifests from age 40 with a peak at 60 years.

In this discussion we will look at the destructive disease process which symbolises multiple myeloma with the aid of our full colour graphics.

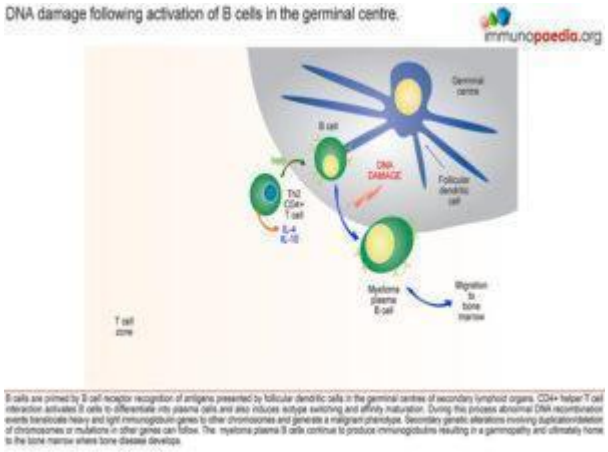
Multiple myeloma



Multiple myeloma is a malignancy of B cells, specifically plasma cells, which is caused by abnormal genetic changes in B cells activated in the post-germinal centre of secondary lymphoid organs. B cells express cell-surface receptors that recognise antigens displayed on follicular dendritic cells in the germinal centres and become primed. CD4 T cell help is then required for differentiation and maturation into antibody-producing plasma cells. In individuals predisposed to multiple myeloma, DNA damage can occur following activation of B cells in the germinal centre. Specifically, abnormal DNA recombination occurs during isotype switching and affinity maturation. This results in translocation of the heavy and/or light immunoglobulin genes to other chromosomes, which influence the regulation of oncogenes or cell-proliferation genes. This primary event generates a malignant phenotype, which can be followed by secondary genetic alterations such as loss or duplication of chromosomes or genetic mutations affecting the expression of tumour-suppressor genes or oncoproteins.

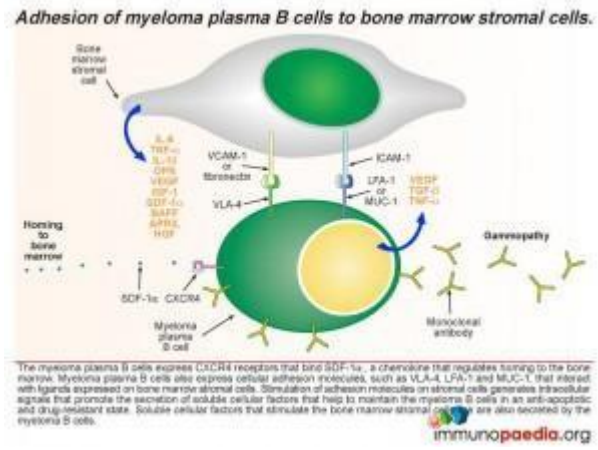
Collectively, the genetic aberrations commonly found include:

1. Translocation of immunoglobulin heavy chain coding regions onto other chromosomes located near proto-oncogenes (c-myc, n-myc and MAF) or cell- proliferation proteins (cyclin D, FGFR3, MMSET).
2. Duplication of chromosomes (3, 5, 7, 9 11 and 21) or loss of chromosomes (13).
3. Mutations in oncoproteins (N-ras and K-ras) or in tumour suppressor genes (p53).



Following the maturation process and isotype switching, myeloma plasma B cells produce monoclonal antibodies, although non-secretory or light chain only forms are known. This can occur with any of the immunoglobulins, IgG being the most common, IgA and IgE occurring intermediately and IgD and IgM occurring rarely; as in this case study (IgM gammopathy).

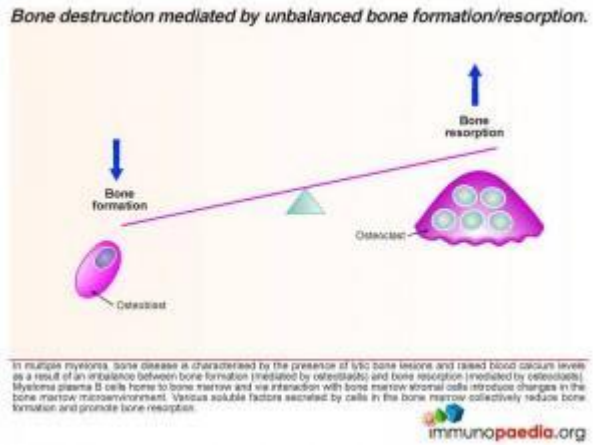
Myeloma plasma B cells constitutively produce monoclonal immunoglobulins resulting in a gammopathy, which can cause amyloidosis due to deposition of excess insoluble proteins. Common sites for this include the tongue, kidneys and heart, as in this presenting case.



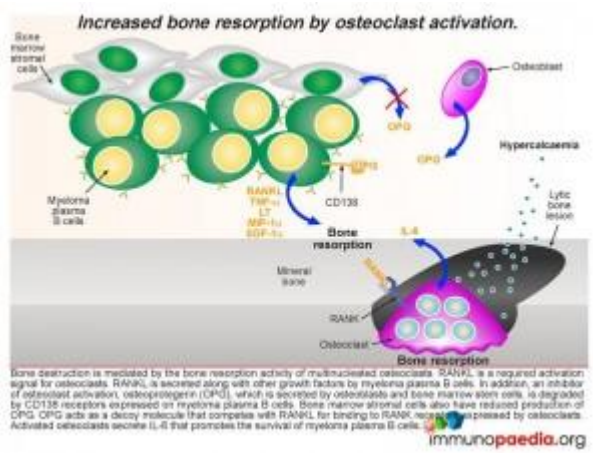
Myeloma plasma B cells migrate to the bone marrow. This homing is regulated by the chemokine stromal cell derived factor-alpha (SDF-1α) binding to the CXCR4 receptor, expressed on the myeloma plasma B cell. The myeloma plasma B cells also express cellular adhesion molecules, which interact with bone marrow stromal cell ligand. This interaction maintains myeloma B cells in an anti-apoptotic state and unresponsive to chemotherapeutic drugs.

The accompanying bone disease is characterised by the presence

of lytic bone lesions that result from an imbalance of bone formation, mediated by osteoblasts, and bone resorption, mediated by osteoclasts, which together remodel the bone microenvironment.

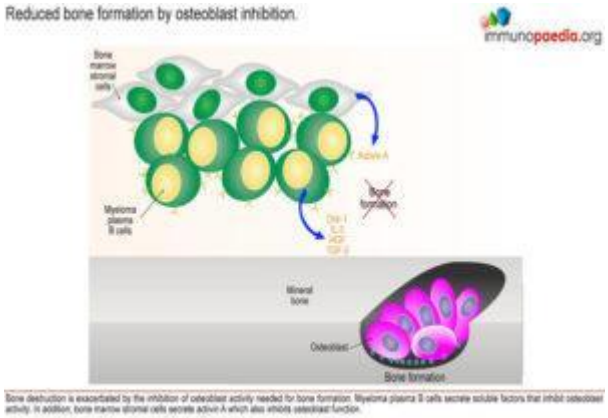


Bone destruction is a hallmark of the disease primarily driven by the activation of multinucleated osteoclasts. This is mediated by stimulation of RANK receptors by RANKL. In addition, the inhibitor of osteoclast activation, osteoprotegerin (OPG), is removed and degraded by CD138 which is expressed on myeloma plasma B cells, resulting in prolonged osteoclast activation.



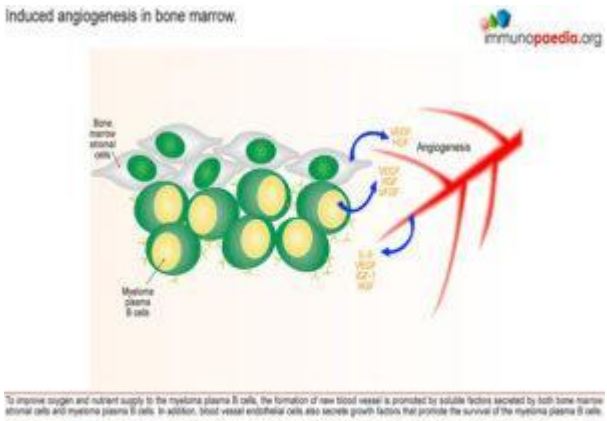
Furthermore, bone formation by osteoblasts is inhibited by soluble factors released by myeloma plasma B cells and the secretion of Activin A from bone marrow stromal cells.

Clinical markers of multiple myeloma



The process of bone resorption creates lytic bone lesions, which liberates calcium phosphates from the mineral bone matrix. This is measurable as hypercalcaemia and hyperphosphataemia in the peripheral blood, as observed in our patient. Lytic bone lesions are visible on X-rays and most often seen on chest X-rays when examining the ribs as well as the skull (where the lesions are seen as a pepper pot skull). The increased number of plasma B cells in bone marrow can be identified from a bone marrow biopsy and are usually present at greater than 10% of the total cells: indicating a neoplastic condition. To confirm the diagnosis, multiple myeloma plasma B cells can be phenotypically characterized as CD38, CD138 and CD56 positive and negative for CD19, CD20 and CD21 expression. Genetic analysis to identify abnormal translocations, loss or duplication of chromosomes or mutations can also be used to confirm the diagnosis.

Since this is a disease of post-germinal centre B cells which implies that the B cells have isotype-switched, the gammopathy usually involves IgG (most common), IgA and IgE monoclonal antibodies and rarely IgD and IgM. In this case study, a rare IgM gammopathy indicates the absence of a class switch following post-germinal activation. We can speculate that the formation of a myeloma plasma B cell phenotype was associated with incomplete heavy chain class switching or may have resulted from aberrant light chain recombination and/or affinity maturation.



The clinical manifestation in this patient was the accumulation of large quantities of antibodies and probable deposition of insoluble complexes of light chains (amyloidosis) in organs such as the tongue, kidney and heart. This was the likely cause of kidney and heart failure, the former indicated by high blood creatinine levels. Immunoglobulin light-chains were also detected in urine samples (Bence-Jones protein) and due to the high turnover of myeloma cells in bone marrow, elevated beta-2-microglobulin shedding occurs and this protein also accumulates to high levels in blood and reflects the staging of the cancer. As seen in our patient, excessive plasma levels of beta-2-microglobulin indicated highly advanced state of disease and poor prognosis. In addition, the large numbers of myeloma B cells probably displaced normal bone marrow haematopoietic cells and disrupted their function, as indicated by bicytopaenia: reduced red cell production (anaemia) and platelet formation (thrombocytopaenia). Disruption of B cell maturation in bone marrow can also impact on humoral immunity and is often related to an increased risk of infection.

When diagnosing multiple myeloma with IgM gammopathy it is important to consider other similar malignant plasma cell medicated diseases as differentials which include Waldenstrom's macroglobulinaemia and monoclonal gammopathy of undetermined significance (MGUS). While MGUS always precedes both multiple myeloma and Waldenstrom's macroglobulinaemia, MGUS does not always

progress to bone marrow involvement. For this reason MGUS alone is not predictive of the onset of multiple myeloma. Differentiating an IgM secreting multiple myeloma from Waldenstrom's macroglobulinaemia is based on the absence of bone disease in the latter. In our case, there was clear evidence of bone disease (X-ray and hypercalcinaemia).

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Treatment

- On admission patient was transfused with three units of packed red cells to correct the anaemia.
- Zoledronic acid (Zometa) was given to control the hypercalcaemia and protect the patient from other skeletal events such as spinal cord compression and pathologic fractures.
- Patient was treated with Decadron 20 mg IV daily (dexamethasone)
- Patient was rehydrated and treated with IV fluids in an attempt to improve her renal function before administration of chemotherapy.
- Plan was to give patient chemotherapy- VAD (vincristine, doxorubicin [Adriamycin], and dexamethasone) to decrease the tumor burden in multiple myeloma. This is typically used in preparation for autologous stem cell transplantation. VAD is administered as a 4-day continuous intravenous infusion of vincristine and doxorubicin, with 4 daily oral doses of dexamethasone.

Patients require a central venous catheter for delivery of the infusion. In selected patients, this therapy can be performed in an outpatient setting.

- Although not administered in this patient Thalidomide is a treatment of choice for multiple myeloma patients.

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Final Outcome

The patient developed renal failure, which remained refractory to treatment. He also developed a cardiac myopathy due to cardiac amyloidosis and died two days later from cardiac failure.

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Evaluation – Questions & answers

What is the diagnosis?

Multiple myeloma, based on clinical history and findings and confirmed on IgM gammopathy, anaemia, hypercalcaemia, urine sample electrophoresis showing positive Bence-Jones protein, presence of >10% plasma B cells in bone marrow aspirate carrying CD38 and CD138 phenotypic markers, elevated Beta-2-microglobulin and lytic bone lesions seen on X-ray.

What is the cause of macroglossia in this patient?

Amyloidosis, due to deposition of excessive amounts of

insoluble immunoglobulin light chains.
What else is linked to the above condition?

Renal failure, which may develop both acutely and chronically. Commonly it is caused by hypercalcaemia due to breakdown of bone but is also due to the tubular damage caused by excretion of light chains (Bence-Jones) proteins and glomerular deposition caused by amyloid, hyperuricemia, or local malignancy infiltrate.
Which cell-type becomes neoplastic and is implicated in multiple myeloma?

Plasma B Cells
What types of genetic aberrations occur in multiple myeloma?

- translocation of immunoglobulin heavy chain coding regions onto other chromosomes located near oncogenes or cell-proliferation proteins
- duplication or loss of chromosomes
- mutations in oncogenes or in tumour-suppressor genes.

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