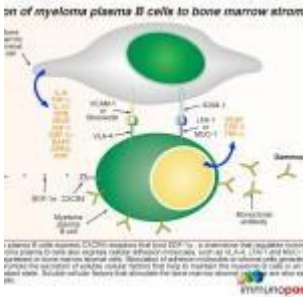


# Case of enlarged hard tongue



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## 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 than 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  $\pm$  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/Haematological

- Some small bruises on arms and legs of various ages
- No rashes
- No petechial 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 x10 <sup>9</sup> /L)
HB	5.4	12.8	10.9	13	(12.1-15.2 g/L)
Platelets	150	129	97	130	(140-450 x10 <sup>9</sup> /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			

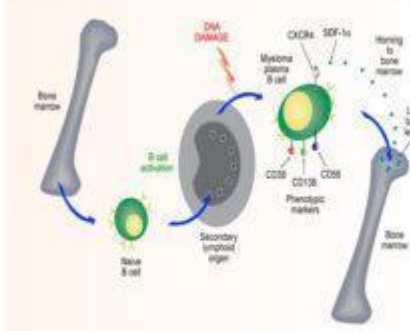
Examination	Value				Normal Limits
Bone Marrow Aspirate-phenotypic markers:					
CD38		Increased levels detected			
CD138		Increased levels detected			
Protein Electrophoresis		M band			

## 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 plasma B cells caused by alterations to genetic material following B cell activation in the germinal centres of secondary lymphoid organs. Genetic effects include primary translocations of immunoglobulin heavy/light chain genes to other chromosomes near oncogenes/cyclin genes and secondary changes including duplications of chromosomes and/or mutations in cell growth/tumour suppressor genes. Myeloma plasma B cells also express CD138 receptors for SDF-1 $\alpha$ , a chemokine that regulates homing to the bone marrow where bone disease develops.

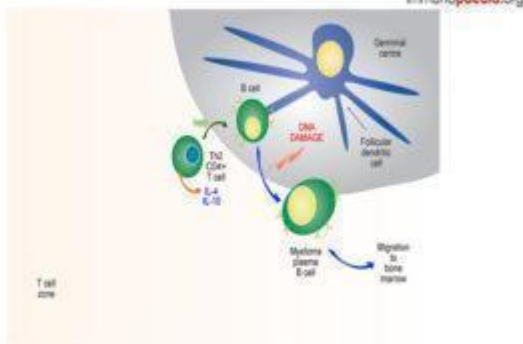
Multiple myeloma is a malignancy of B cells, specifically plasma cells, which is caused by abnormal genetic changes in B cells activated in the post-germinal centre of secondary lymphoid organs. B cells express cell-surface receptors that recognise antigens displayed on

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).

DNA damage following activation of B cells in the germinal centre.



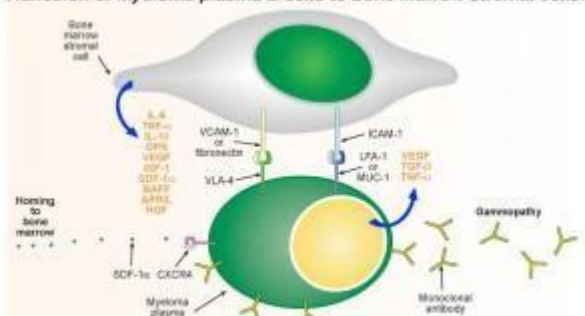
B cells are primed by B cell receptor recognition of antigens presented by follicular dendritic cells in the germinal centres of secondary lymphoid organs. CD4+ helper T cell interaction activates B cells to differentiate into plasma cells and also induces isotype switching and affinity maturation. During this process abnormal DNA recombination events translocate heavy and light immunoglobulin genes to other chromosomes and generate a malignant phenotype. Secondary genetic alterations involving substitution of chromosomes or mutations in other genes can follow. The myeloma plasma B cells continue to produce immunoglobulins resulting in a gammopathy and ultimately home to the bone marrow where bone disease develops.

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.

Adhesion of myeloma plasma B cells to bone marrow stromal cells.



The myeloma plasma B cells express CXCR4 receptors that bind SDF-1 $\alpha$ , a chemokine that regulates homing to the bone marrow. Myeloma plasma B cells also express cellular adhesion molecules, such as VLA-4, LFA-1 and MUC-1, that interact with ligands expressed on bone marrow stromal cells. Stimulation of adhesion molecules on stromal cells generates intracellular signals that promote the secretion of soluble cellular factors that help to maintain the myeloma B cells in an anti-apoptotic and drug-resistant state. Soluble cellular factors that stimulate the bone marrow stromal cells are also secreted by the myeloma B cells.

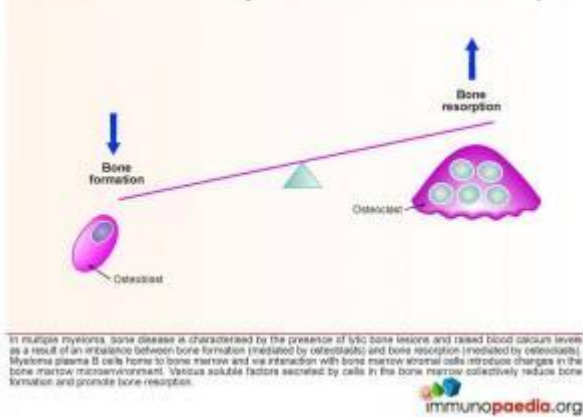
Myeloma plasma B cells migrate to the bone marrow. This homing is regulated by the chemokine stromal cell derived factor-alpha (SDF-1 $\alpha$ ) binding to the [CXCR4](#) receptor, expressed on the myeloma plasma B cell. The myeloma plasma B cells also express cellular adhesion molecules, which interact 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



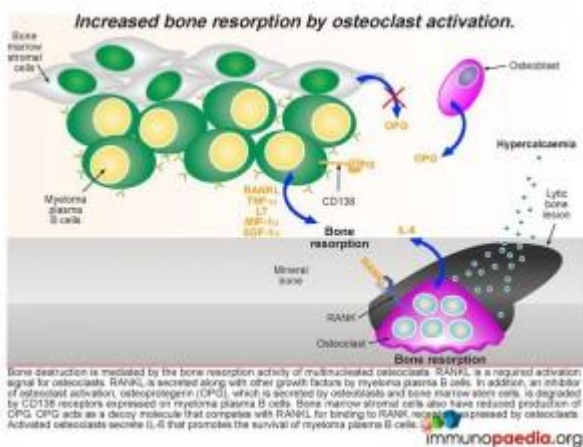
of lytic bone lesions that result from an imbalance of bone formation, mediated by osteoblasts, and bone resorption, mediated by osteoclasts, which together remodel the bone microenvironment.

*Bone destruction mediated by unbalanced bone formation/resorption.*



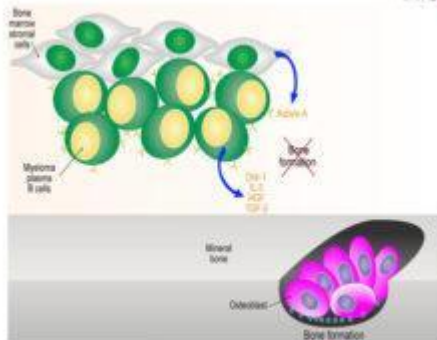
Bone destruction is a hallmark of the disease primarily driven by the activation of multinucleated osteoclasts. This is mediated by stimulation of [RANK receptors](#) by [RANKL](#). In addition, the inhibitor of osteoclast activation,

[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.

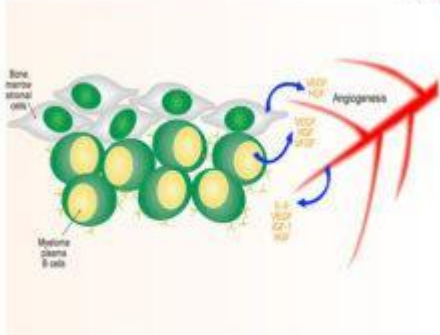
## Clinical markers of multiple myeloma



Bone resorption is exacerbated by the inhibition of osteoblast activity needed for bone formation. Myeloma plasma B cells secrete soluble factors that inhibit osteoblast activity. In addition, bone marrow stromal cells secrete osteostatin which also inhibits osteoblast function.

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.



To improve oxygen and nutrient supply to the myeloma plasma B cells, the formation of new blood vessels is prompted by soluble factors secreted by both bone marrow stromal cells and myeloma plasma B cells. In addition, blood vessel endothelial cells also secrete growth factors that promote the survival of the myeloma plasma B cells.

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 bicytopenia: reduced red cell production (anaemia) and platelet formation (thrombocytopenia). Disruption of B cell maturation in bone marrow can also impact on humoral immunity and is often related to an increased risk of infection.



List of abbreviations for soluble factors

LPS	Lipopolysaccharide
IL-1	Interleukin 1 beta
IL-6	Interleukin 6
IL-8	Interleukin 8
GM-CSF	Granulocyte-macrophage colony-stimulating factor
OPG	Osteoprotegerin
OPG-R	Osteoprotegerin receptor
PDGF	Platelet-derived growth factor
VEGF	Vascular endothelial growth factor
CSF-1	Colony-stimulating factor 1
CSF-2	Colony-stimulating factor 2
CSF-3	Colony-stimulating factor 3
CSF-4	Colony-stimulating factor 4
CSF-5	Colony-stimulating factor 5
CSF-6	Colony-stimulating factor 6
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CSF-100	Colony-stimulating factor 100

When diagnosing multiple myeloma with IgM gammopathy it is important to consider other similar malignant plasma cell mediated 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 hypercalcaemia).

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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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