THE NORTHERN HOSPITAL

MULTIPLE MYELOMA

Brazilian Blue Morpho Butterfly, oil on canvas, Martin Johnson Heade 1864

It has been said that something as insignificant as the flutter of a butterfly's wing in Brazil can ultimately result in a tornado on the other side of the world.

In 1812 Napoleon Bonaparte had assembled the greatest army in history, "Le Grande Armee" of over 600,000 men, in preparation for an invasion of the Russian Empire. An army of this size would not be surpassed until the Great War of the next century. It seemed to the rest of Europe that the fall of the Tsar was imminent and Napoleon's dominance over Europe would be complete and unchallenged. He was supremely confident in his eventual victory. In the same year Napoleon's compatriot, the greatest mathematician of the age, the Marquis Pierre-Simon de Laplace had published his famous essay on the "deterministic universe". Laplace speculated that if at one particular instant in time, the exact position and velocities of all the objects in the universe, as well as the forces that were acting on them at that instant could be known, the entire future history of the universe could be predicted exactly – the universe was in other words entirely preordained or deterministic – but only the mind of God could know these exact parameters of nature at any given moment. Napoleon's planning had been meticulous as always – he had put in place the exact parameters that were required of victory – in a deterministic universe his victory was assured. As Alexander was reassured by the oracle of Delphi prior to his invasion of the Persian Empire, so Napoleon, a child of the "Enlightenment" would have been reassured by his great mathematician.

History records however that Napoleon's invasion of Russia ended in disastrous defeat. There was one parameter that Napoleon had not taken into account. It would not be the Russians that defeated the Grande Armee, it would be nature. He had not seriously taken into consideration two factors that were largely unpredictable at the time- the harshness of the Russian winter of 1812 and the specter of disease in the form of typhus. The idea of a deterministic universe remained strong – you just had to take into account ***all*** *the relevant parameters - until the 1890s when another great French mathematician Henri Poincare conjectured that parameters on the very small scale could never be exactly known to a degree that would enable accurate prediction in a dynamic system. The thinking until this time said that things could be measured to a degree of accuracy that although the exact outcome could not be predicted, the final result would be so close as to not really matter in practical terms. Poincare was not so sure however, in any event he lacked the computer power to prove his theories in a rigid mathematical sense.*

This computing power would not become available until the Twentieth century. In 1961 a serendipitous cup of coffee led the meteorologist Edward Lorenz to conclude that the deterministic universe was out of the reach of human understanding. He had been running a computer program to predict weather patterns, aiming to reproduce some results he had previously obtained. While the computer was left running doing its complex calculations he went for a cup of coffee to await its results. When he returned he was stunned to find that it had produced markedly different results than had been obtained previously. He was most perplexed until he finally realized that one of the parameters he had fed into the computer was rounded to an approximation – however this was of the order of only 0 .002 percent difference in initial conditions! For a system as complex as atmospheric weather patterns, this was enough to have flow on effects of the most dramatic consequences. He concluded that a system as complex as weather patterns could never be predicted for much more than a week, because the accuracy of

the initial conditions that needed to be recorded to predict that far ahead were beyond the measuring capabilities of any technology. This realization was the foundation stone upon which "chaos" theory would be formulated. He described his findings in a famous paper in 1972, entitled "Predictability: Does the flap of a butterfly's wings in Brazil set off a tornado in Texas?" This contradicted the view that although exact initial conditions could not be determined in complex systems, they could be determined near enough to confirm the old Laplacian idea of a deterministic universe. A sprinter for example who started a tenth of a second after the gun had fired would break the tape only a tenth of a second after what he would have achieved – not necessarily! Lorenz demonstrated mathematically that seemingly most insignificant changes in the initial parameters of a complex system could have the most profound consequences later on, so much so as to defy all possibility of accurate prediction. He described this idea in his famous "butterfly effect" analogy. The mere flap of a butterfly's wing in Brazil, although not directly providing the energy for it, could set in train a complex series of atmospheric consequences that eventually results in a tornado on the other side of the world!

The death knell of the deterministic universe was actually sounded even before Lorenz at a meeting of some of the Twentieth Century's most brilliant physicists that included Albert Einstein, Marie Curie and Niels Bohr, known as the Fifth Solvay conference of 1927. Seventeen of the twenty nine invited physicists would receive Nobel Prizes. They debated and formulated the theory of quantum mechanics. From this work Werner Heisenberg, in his famous "uncertainty principle" determined that on the atomic or "quantum scale" things existed only as "probabilities" not as concrete certainties! Neils Bohr exclaimed that "those who are not shocked when they first come across quantum theory have not understood it!" Einstein even had difficulty accepting the new theory, "God does not play dice!" he once famously quipped. The "father of the atomic bomb" J. Robert Oppenheimer wrote "There was terror as well as exultation in this new insight". Heisenberg determined that on the smallest possible scale in the "quantum world", the velocity (or momentum) of a particle as well as its exact position could never been known at the same time. Only one of these parameters could be known at any given instant, either its position or its momentum. On the ultimate quantum scale the universe therefore cannot be deterministic in the Laplacian sense; on the large scale something may be extremely probable but it can never be certain. Napoleon's "victory" in 1812 was never "assured".

The debate begun by Laplace has continued to evolve over the centuries and two things have now become clear, we do not live in a rigidly pre-ordained Universe, and the most inconsequential "flap of a butterfly's wing" may indeed have the most profound and unforeseen consequences into the future. In the complex biological world, the merest and seemingly inconsequential butterfly flap of a miniscule change in the sequence of amino acids within a strand of DNA of a single cell, may lead to the profoundest changes on the macroscopic level. No better example is given than in malignant disease. A single minute genetic alteration can create the tornado of a life threatening disease. It is a sobering thought that in our medical practice it is not always the spectacular or interesting patient we should be concerned with. The most seemingly inconsequential oversight, the noting of unexplained proteinuria or back pain for example, may lead to the profoundest of consequences for the patient.

MULTIPLE MYELOMA

Introduction

Multiple myeloma is a disorder of the blood in which **malignant plasma cells** accumulate in the bone marrow and produce an **abnormal immunoglobulin**, which is usually a monoclonal IgG or IgA.

It is characterized in particular by **skeletal destruction**, **renal failure**, **anemia**, and **hypercalcemia.**

Multiple myeloma can have a wide range of complications and clinical presentations.

The diagnosis is frequently not considered on initial presentation.

Important presenting problems to the ED in older age groups which should prompt consideration of multiple myeloma, include unexplained:

1. **Hypercalcemia**
2. **Renal failure**
3. **Anaemia**
4. **Bone pain**
   - **Severe osteoporosis/ bone fractures**
5. **Proteinuria**
6. **Recurrent infections.**

If multiple myeloma is suspected the initial screening investigations should include:

1. **Urinalysis for Bence-Jones proteinuria**
2. **Plasma protein electrophoresis**
3. **Radiological imaging.**

If abnormal proteins are detected by **plasma protein electrophoresis**, the patient will require further specialist investigation to distinguish **multiple myeloma** (a malignant condition) from a "**monoclonal gammopathy of uncertain significance",** (or "MGUS", a more benign condition, although there is a longer term risk).

Usually a bone marrow biopsy will be undertaken to establish a definitive diagnosis.

All patients suspected of having multiple myeloma should be referred to a Haematologist.

Epidemiology

Multiple myeloma is generally a disease of older adults.

- The median age at diagnosis is 66 years
- 10 % of cases are diagnosed < 50 years.
- Only around 2 % of cases are younger than 40 years.

Pathophysiology

The exact cause of multiple myeloma is unknown.

The first pathogenetic step in the development of myeloma is the emergence of a limited number of clonal plasma cells, clinically known as monoclonal gammopathy of undetermined significance (or **MGUS**). Patients with MGUS do not have symptoms or evidence of end-organ damage, but they do have an annual *risk* of 1 % of progression to myeloma or a related malignant disease.

Multiple myeloma can cause a wide variety of complications:

1. Hematological:

   Blood cell components:

   The proliferation of plasma cells may interfere with the normal production of blood cells, resulting in:

   - Anemia
   - Leukopenia
   - Thrombocytopenia

   Hyperviscosity:

   - Occasionally, some patients may have such a high volume of monoclonal protein in their blood that increased viscosity results in vaso-occlusive complications such as stroke or ACS.

2. Plasmacytomas:

   The malignant plasma cells may cause:

   - Soft-tissue masses (plasmacytomas)

- Bony lytic lesions.

3. Bone:

   Complications may include:

   - Multiple discrete lytic lesions, with bone pain and hypercalcemia
   - Vertebral crush fractures, which may lead to spinal cord compression.
   - Areas of diffusely reduced bone density.

     Diffuse osteopenia may suggest myelomatous involvement even before discrete lytic lesions become apparent.

4. Renal failure:

   - Renal failure is a common complication

5. Impaired immunity:

   - The aberrant antibodies that are produced lead to impaired humoral immunity, and patients have a high prevalence of infection, especially with encapsulated organisms such as Pneumococcus.
   - The overproduction of these antibodies may also lead to hyperviscosity amyloidosis, and renal failure

6. Hypercalcemia.

7. Secondary amyloidosis

Prognostic features

Features which correlate directly with the presence of the total mass of myeloma cells and that have prognostic value include:

- Bone lesions
- Hypercalcemia
- Anaemia

Clinical features

Patient symptoms for **multiple myeloma** may range from asymptomatic in the early stages of disease to acutely life-threatening.

Important clinical presentations to the ED of patients with multiple myeloma may include the following:

The most common 4 presentation entities are described by the acronym "**CRAB**"

1.. Symptoms related to hyper**c**alcemia:

These may include:

- GIT upset: nausea, vomiting, constipation.
- Dehydration
- Confusion

2. Unexplained acute on chronic or chronic **r**enal failure:

- Renal impairment occurs in 20 - 40 % of newly diagnosed patients with myeloma, and is typically due to light chain deposition within the distal and collecting renal tubules or hypercalcaemia.

3. **A**naemia:

- Unexplained anemia:

  Anaemia is found in approximately 70% of those with newly diagnosed myeloma.

4. Unexplained **b**one pain:

- Lytic bony metastases

  This is the most common presenting symptom in multiple myeloma.

  Bony pain is a relatively common symptom, particularly back pain, occurring in up to 58% of patients.

  Lytic lesions are detectable in almost 80% of patients at diagnosis.

  Those with more advanced disease may present with a **pathological** fracture from minimal trauma

Other presentations can include:

5. Impaired immunity:

- Recurrent infection (> 2 per year)

- Infection with unusual organisms

6. Neurological symptoms:

Confusion, seizure, altered conscious state:

- **Cerebral metastases** and **hypercalcemia** will need to be excluded.

Spinal cord symptoms:

- Vertebral destruction and spinal cord compression will need to be excluded.

7. **Febrile neutropenia**:

- For those already on **chemotherapy** or **immunosuppressives febrile neutropenia** is an ever present threat.

  This must always be kept in mind for any patient receiving these agents.

Differential Diagnoses:

Distinguishing **symptomatic** myeloma, which **typically requires treatment**, from asymptomatic **precursor** conditions can be difficult.

By definition, patients with **MGUS, light chain monoclonal gammopathy of uncertain significance** and **smoldering multiple myeloma** and are **asymptomati**c.

These conditions may become apparent when routine blood tests reveal an elevated total protein and globulin, and subsequent serum electrophoresis demonstrates a **monoclonal paraprotein.**

These patients may ultimately progress to symptomatic myeloma and so require careful monitoring.

Criteria for these precursor conditions are as follows:

Monoclonal gammopathy of undetermined significance (MGUS) is defined as:

- A serum paraprotein of < 30 g/L

With

- A marrow plasma cell infiltrate of < 10 %.

And

- No symptoms or end organ damage

Smoldering multiple myeloma is defined as:

- A serum paraprotein of > 30 g/L

Or

- A bone marrow plasmacytosis of > 10 %

And

- No symptoms or end organ damage

Light chain monoclonal gammopathy of uncertain significance is defined as:

- Abnormal free light chain ratio (< 0.26 mg/L or > 1.65 mg/L)
- Increased level of the appropriate involved light chain (i.e, increased kappa light chains in patients with ratio > 1.65 mg/L, and increased lambda light chains in patients with ratio < 0.26 mg/L)
- Clonal plasma cells < 10 %
- Urinary monoclonal protein < 500 mg/24 hours
- No immunoglobulin heavy chain expression on immunofixation
- Absence of end organ damage attributable to the plasma cell disorder

Staging;

The **Revised International Staging System** for myeloma is as follows:

STAGE	DEFINITION (ALL CRITERIA MUST BE MET)	5 YEAR SURVIVAL
I	Serum albumin > 35 g/L Serum β-2 microglobulin < 3.5 mg/L None of the following high risk cytogenetics: • t(4;14)	82 %

	● t(14;16) ● del(17p) Normal serum lactate dehydrogenase	
II	Not fitting Stage I or III	62 %
III	Serum β-2 microglobulin > 5.5 mg/L High risk cytogenetics *or* elevated serum lactate dehydrogenase	40 %

Investigations

Blood tests

1. FBE:
   - For **anaemia**
     - ♥ This is typically normochromic and normocytic.
     - ♥ Occasionally it can be macrocytic.
2. U&Es/ glucose:
   - For renal impairment/ failure. .
3. Serum calcium / phosphate / magnesium:
   - Check for **hypercalcemia**

     If found, *alternative* etiologies should be excluded with **parathyroid hormone (PTH**) levels, which should be **suppressed** in response to the hypercalcaemia.

     Vitamin D levels should also be checked.
4. LFTs
   - Albumin level is an important parameter in staging.

5. Uric acid:

- Uric acid levels will be high if the patient has high cell turnover.

6. **Protein electrophoresis**:

Protein electrophoresis of serum is a sensitive means of detecting the abnormal monoclonal proteins that are found in myeloma.

Where the diagnosis has not already been established, serum and urine protein electrophoresis studies are the best initial investigations.

Identification of the exact immunoglobulin isotype of the paraprotein can be done. These can be:

- IgG
- IgA
- IgM, (less commonly)

Other isotypes are rare.

- The exact identity of the isotype is important in differentiating whether production of the paraprotein is by a clonal plasma cell disorder, or by a clonal lymphoproliferative condition.
- An IgM paraprotein is very uncommon in myeloma. It is more indicative of a clonal **lymphoproliferative disorder,** such as low-grade non-Hodgkin's lymphoma.

  Waldenstrom's macroglobulinaemia is an example of one form of low-grade non-Hodgkin's lymphoma that is characteristically associated with a serum IgM paraprotein.

7. β2-microglobulin levels:

- This is used by Hematologists in staging

Urinalysis:

FWT will show proteinuria

Bence-Jones protein is found in the urine. It is a homogeneous kappa or lambda *free light chain.*

Urine should also be sent for microscopy and culture, when UTI is suspected.

Plain Radiology:

Plain radiography may detect bony myelomatous lytic deposits.

A **skeletal survey** with plain radiographs has been the *initial* imaging modality of choice for suspected multiple myeloma.

A major distinction between myeloma and monoclonal gammopathy of uncertain significance is increased lysis of bone resulting from the activation of osteoclasts by myeloma cells.

In myeloma a skeletal X-ray survey will commonly show:

- Multiple discrete lytic lesions.
- Vertebral crush fractures
- Areas of diffusely reduced bone density.

These findings are some of the most important means for detecting the **malignant** characteristics of myeloma.

CT Scan

There should be a low threshold for **cerebral CT scanning** in any patient known to have multiple myeloma and who presernts with **headache, altered conscious state** or **confusion**.

Cerebral metastases will need to be excluded.

For screening / staging purposes, multidetector CT has the advantage of superior sensitivity for the detection of bone lesions.

MRI

Magnetic resonance imaging is the most sensitive investigation, for lytic bony lesions, and may be used to identify these in suspicious cases when plain radiology skeletal survey fails to yield a diagnosis.

The magnetic resonance imaging method of choice is the **short-tau inversion recovery** (or "**STIR"**) This is the most sensitive method to identify lytic lesions.

Bone scan

Bone scanning *lacks specificity for myeloma* and so is **not** a suitable alternative to radiological examination.

Bone marrow biopsy

A bone marrow aspirate and biopsy establishes the definitive diagnosis of myeloma.

It provides a *direct measure* of the degree of plasma cell infiltration in the bone marrow.

In myeloma there is an abnormally high percentage of plasma cells (> **10%**), compared to an approximately normal percentage in monoclonal gammopathy of uncertain significance.

Management

Management in the ED:

Management issues in the ED will of course depend on the exact nature of the presenting problem.

Patients may already be diagnosed with multiple myeloma or this disease may be suspected but as yet undiagnosed.

The commonest scenarios requiring **intervention in the ED** in patients with multiple myeloma will include

1. **Sepsis**:
    - Including cases of **febrile neutropenia** for those on chemotherapeutic agents or immunosuppressives.
2. **Hypercalcemia**:
    - Including treatment for **dehydration,** which is a significant complication of hypercalcemia
3. **Hyperkalemia**:
    - Secondary to acute on chronic renal failure.
4. **Symptomatic anaemia**
5. **Bone pain**:
    - Radiation therapy may be required to treat painful bony lesions refractory to pain medication or spinal cord compression
6. Pathological fractures
    - These will often require treatment with a combination of surgical fixation and radiation therapy.

Specific management:

Patients can be divided in two main groups: patients who are considered eligible for autologous stem cell transplantation and those considered ineligible.

This distinction is somewhat arbitrary, but age, frailty and comorbidities are part of the clinical decision making process.

In *general* terms:

Symptomatic myeloma usually requires immediate treatment.

For those **< 65 years of age**, or those aged **65 - 70 with few comorbidities**, **autologous stem cell transplantation is the current standard**

Patients typically receive 3 - 6 cycles of induction treatment, aiming to achieve a complete or near complete response, prior to receiving their transplant.

There have been significant recent advances in the choice of induction agents and several new agents that have improved responses in multiple myeloma are now available.

The best results appear to be achieved with combinations of:

1. Steroids

2. Cytotoxic chemotherapy (such as **cyclophosphamide** or **doxorubicin**)

3. A novel immunomodulatory agent:

   - **Thalidomide** or **lenalidomide**

   Or

   - A proteasome inhibitor (e.g. **bortezomib**).

Following transplant, patients are often offered maintenance thalidomide, with or without prednisone, for approximately 12 months.

Those ineligible for transplant may be treated with a combination of steroids, a cytotoxic agent (such as cyclophosphamide) and thalidomide or bortezomib. The role of maintenance therapy following induction treatment remains unclear in this group.

Disposition:

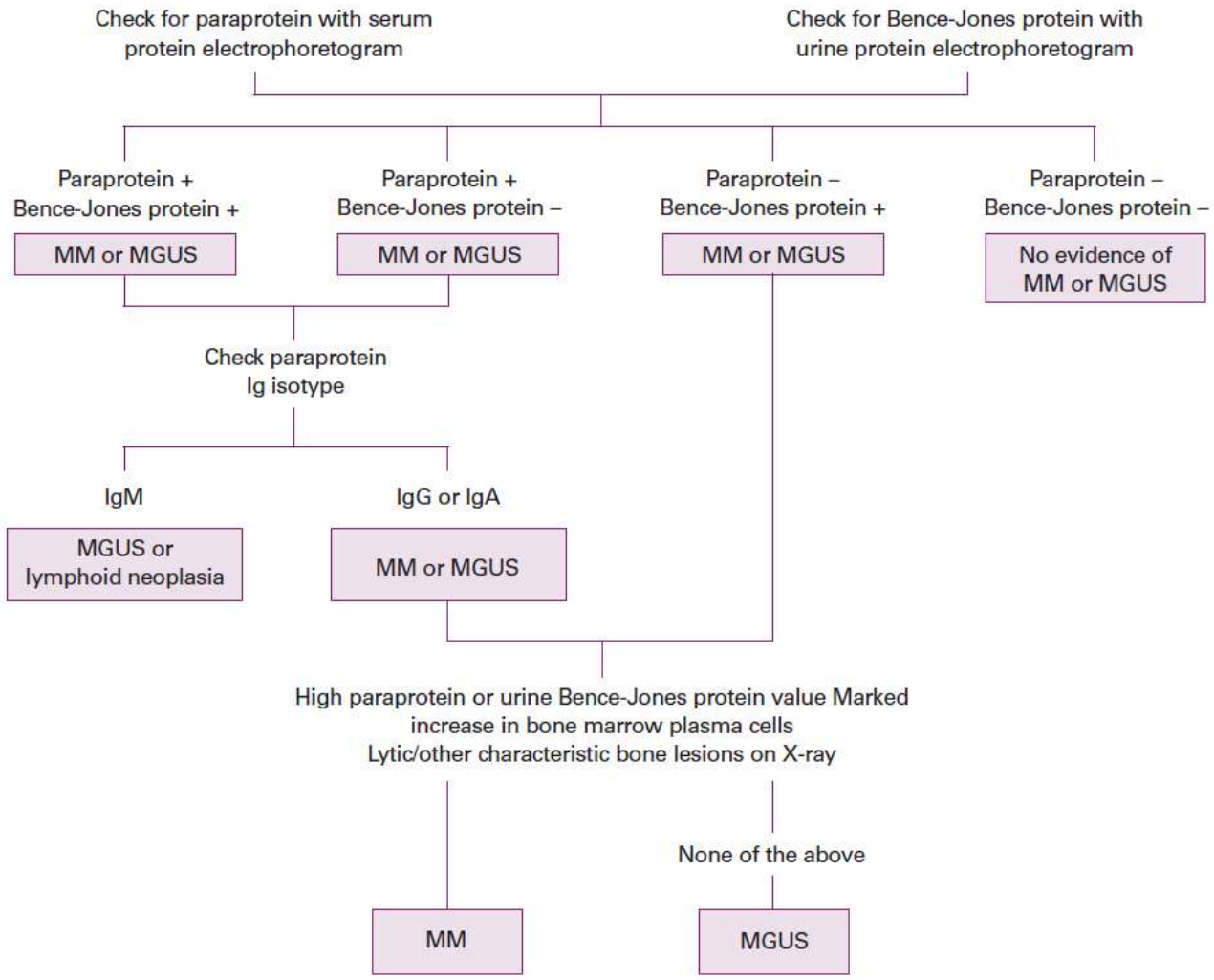
Most patients who present with complications of their multiple myeloma will require specialist consultation with:

- Haematology
- Oncology

Appendix 1

Initial screening testing for multiple myeloma

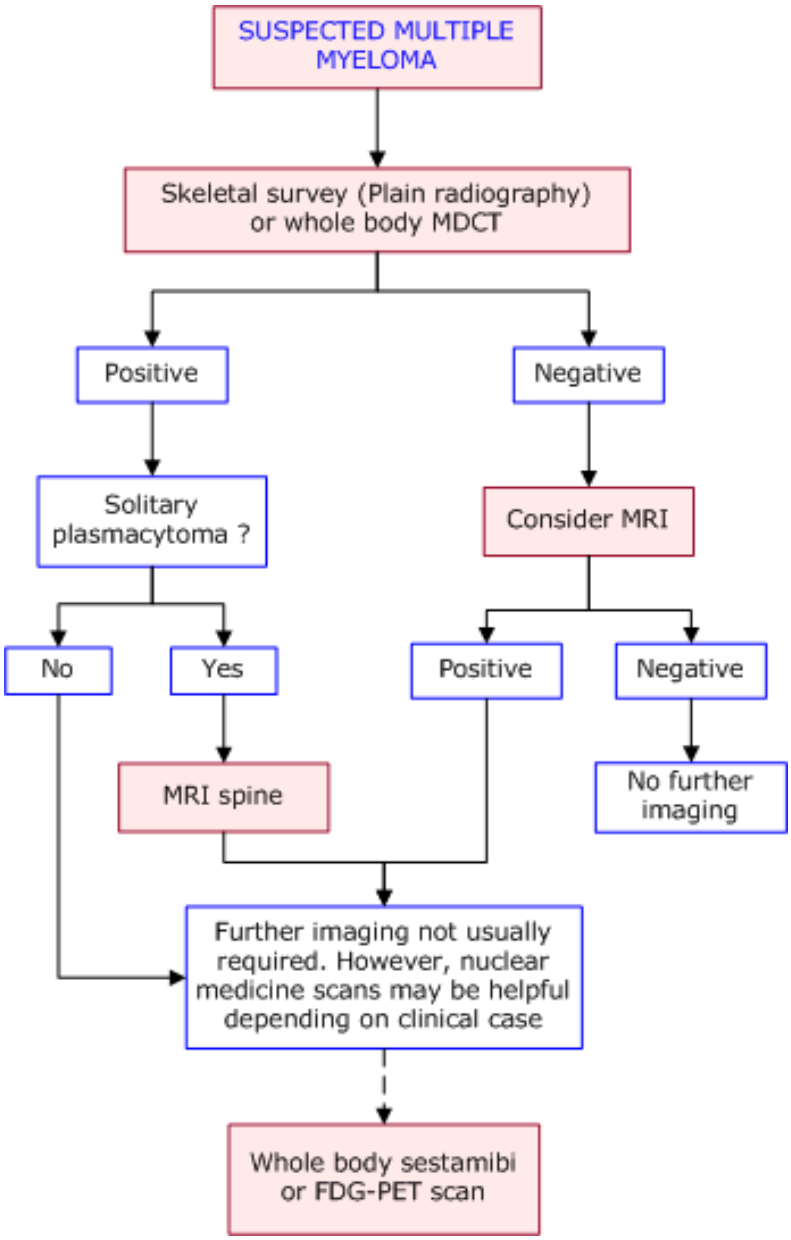
Screening and diagnosis of multiple myeloma



MM multiple myeloma
MGUS monoclonal gammopathy of uncertain significance
Ig immunoglobulin

Appendix 2

Imaging pathway for suspected multiple myeloma [2]



Appendix 3

Plain Radiograph: Lateral skull x-ray showing the typical multiple small punched out lesions characteristic of multiple myeloma, (www.imagingpathways.health.wa.gov.au)

Left: Magnetic Resonance Imaging (Sagittal T1 and STIR) images showing extensive myelomatous infiltration of the lower thoracic and lumbar spine

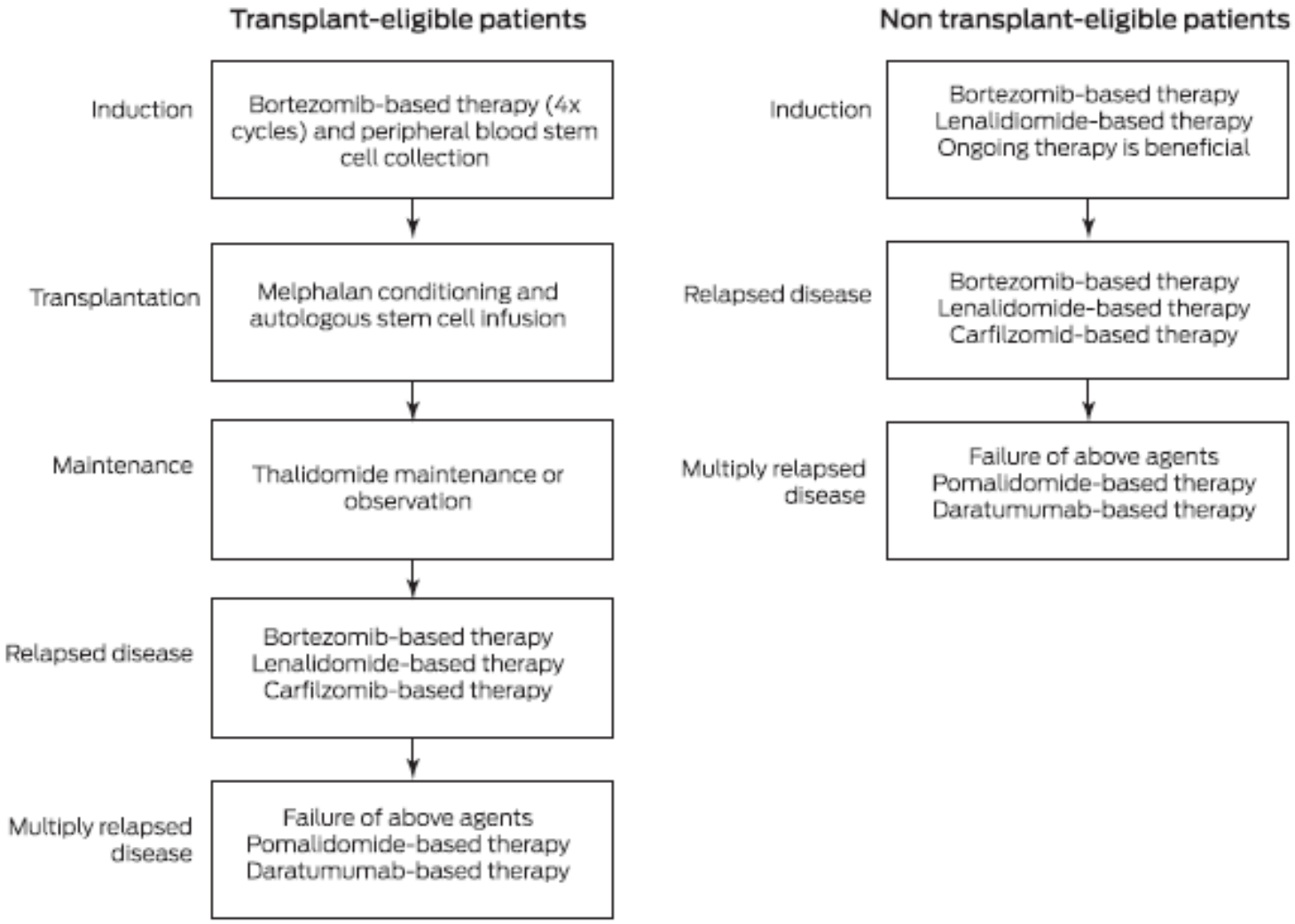
While a skeletal survey with plain radiographs is still considered the initial imaging modality of choice, Multidetector CT has the advantage of superior sensitivity for the detection of bone lesions and has a much more rapid acquisition time

MRI is also highly sensitive but is generally reserved for symptomatic patients with negative skeletal surveys

Current guidelines suggest that nuclear medicine scans such as Sestamibi and FDG PET should not be routinely used in diagnosis but may be useful to clarify previous imaging findings in selected cases.

(www.imagingpathways.health.wa.gov.au)

Appendix 4



Overview of current therapeutic options for Australian patients with myeloma. [3]

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