Retrospective review of multiple myeloma and immunosecretory disorder cases diagnosed in a tertiary setting

HF Visser MBChB(Pret)
Senior Registrar, Department Orthopaedic Surgery, University of Pretoria
A Visser MBChB(Pret)
Senior Registrar, Department Clinical Pathology, University of Pretoria, National
CH Snyckers MBChB, MMed(Orth)(Pret)
Consultant, Department Orthopaedic Surgery, University of Pretoria
R Goller MBChB(Pret)
Senior Registrar, Department Orthopaedic Surgery, University of Pretoria
R Pool, MBChB(Pret), MMed(Haemat)
Head of Department, Department Haematology, University of Pretoria,
National Health Laboratory Service TAD
JG Myburgh MBChB, MMed(Orth)(Pret)
Acting Head of Department, Department Orthopaedic Surgery, University of Pretoria

Reprint requests:
Dr A Visser
adele@up.ac.za

Abstract
Purpose of the study: Despite the relatively high incidence of multiple myeloma reported worldwide, South African statistics seem to be significantly lower. Our purpose in doing this study was to determine whether patients with suspected immunosecretory disorders are being appropriately evaluated and followed up. Secondary purposes include an impression of the most common clinical features prompting investigation as well as the stage of disease at time of diagnosis.

Description of methods: All patients investigated for immunosecretory disorders by serum or urine electrophoresis over a 4-year period were included in this study. Each patient’s laboratory and radiological data were evaluated to determine the true diagnosis, and assess the comprehensiveness of the investigation.

Summary of results: In total, 582 patients were included – 39 patients had multiple myeloma (6.7%). A single case of plasmacytoma and plasma cell leukaemia was identified. Waldenström’s macroglobulinaemia was identified in seven patients (1.2%) and monoclonal gammopathy of undetermined significance (MGUS) in 83 patients (14.3%). Due to the risk of progression from MGUS to multiple myeloma, patients need to be re-evaluated biannually, shown to be the case in only 11% of cases.

Of all the malignant disorders (48 cases) the majority of patients were diagnosed in an orthopaedic setting (45%), followed by internal medicine (39%). Radiological abnormalities were the most common clinical finding prompting investigation, with lytic lesions or osteoporosis seen in 50%, pathological fractures in 17% and neurological manifestations noted in 18% of cases.

The majority of patients who could be staged were diagnosed at a relatively late stage of disease, rendering the prognosis worse than in early disease. This suggests a relatively low index of suspicion in our clinical setting.

Conclusion: Multiple myeloma and related disorders are commonly encountered in the orthopaedic setting. Although the sample size is small, this data suggests that patients are diagnosed late in disease progression and often not evaluated appropriately. A clear protocol should be established to actively exclude this diagnosis if it is suspected.
Introduction

For a number of reasons, multiple myeloma and immunosecrorytary disorders are of great importance to orthopaedic surgeons. A large proportion of these patients can present primarily to the orthopaedic surgeon due to pathological fractures (present in up to 80% of this population), bone pain and/or osteopaenia.1 The role of the orthopaedic surgeon in the management entails a high index of suspicion with appropriate investigation and referral. Impending and complete fractures should be surgically stabilised and irradiated. Irradiation can also be used for palliation of pain and treatment of neurological symptoms.2 Of note, surgery in this population group is likely to be complicated as the gammopathy may compromise organ function, presenting as renal dysfunction, coagulopathies, etc.

The WHO defines multiple myeloma (plasma cell myeloma, myelomatosis, Kahler’s disease) as a multifocal, bone marrow-based neoplasm, associated with an M-protein in serum and/or urine and end organ damage.4 In Caucasian populations, it accounts for roughly 1% of all malignancies and just over 10% of haematological malignancies.5 This is generally considered a disease of the elderly, with less than 2% of cases occurring in patients younger than 40 years of age.5 Various risk factors have been identified, including exposure to radiation, benzene and other organic solvents; insecticides and herbicides may also play a role.11 Chronic inflammatory conditions have been suggested to facilitate the progression of B-cell dyscrasias;12 but conflicting data exists.13 It has been postulated that HIV-1 infection may indirectly increase the risk of this malignancy by its nature of chronic immune stimulation.1 This, however, has been refuted by some studies, which have not been able to show an increased incidence within a South African HIV-1 infected population.1 Multiple myeloma accounted for 0.43% of cases of newly diagnosed malignancies in South Africa in 1999, with an absolute number of 257 cases (130 females to 127 males).14 This makes the reported incidence 0.00054% in the South African population of 47.8 million people.14 The reported incidence in the UK, with a population of 58.8 million people in 2001,15 is 0.036%.16 The UK incidence is therefore 67 times higher than that of South Africa. In light of the fact that no clear aetiology is known at present, this data suggests that it is likely that multiple myeloma is under-diagnosed in South Africa. Despite multiple new treatment modalities,17 it remains largely incurable, even after stem cell transplant.8

The World Health Organization (WHO) defines monoclonal gammopathy of undetermined significance (MGUS) as the presence of an M-protein, quantified as less than 30 g/L, bone marrow clonal plasma cells, quantified to less than 10% and the absence of any end organ damage (CRAB: hypercalcaemia, renal insufficiency, anaemia, bone lesions).4 If there is no end organ damage, but the monoclonal band is in excess of 30 g/L, a diagnosis of asymptomatic or smouldering multiple myeloma can be made.12,10 It is important that any other causes known to produce M-proteins (see Table 1) should be excluded. Although this condition signifies a clonal process, it is not considered as neoplastic per se as it does not always progress to malignancy.1 The overall risk of progression to overt malignant disease has been determined to be 10% at 10 years with increased risk thereafter,18 depending on risk factors2 like band sizes exceeding 15 g/L, IgA or IgM subtype, high plasma cell percentage in bone marrow and abnormal free light chain ratios.9 For this reason, patients should be monitored every 6 to 12 months for possible progression.7,20

Table 1: World Health Organization (WHO) diagnostic criteria from 2003 and 2008

<table>
<thead>
<tr>
<th>WHO CRITERIA 2003</th>
<th>WHO CRITERIA 2008</th>
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<tr>
<td><strong>Major criteria</strong></td>
<td>1. M-protein in serum or urine (no levels stipulated)</td>
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<tr>
<td>1. Plasmacytoma on tissue biopsy</td>
<td>2. Bone marrow clonal plasma cells or plasmacytoma</td>
</tr>
<tr>
<td>2. Bone marrow infiltration with &gt;30% plasma cells</td>
<td>3. Related organ or tissue impairment</td>
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<tr>
<td>3. Monoclonal globulin spike on serum</td>
<td>- C ⇒ Hypercalcaemia</td>
</tr>
<tr>
<td>- IgG &gt;35g/L</td>
<td>- R ⇒ Renal impairment</td>
</tr>
<tr>
<td>- IgA &gt;20g/L on urine</td>
<td>- A ⇒ Anaemia</td>
</tr>
<tr>
<td>- &gt;1g/24hours kappa or lambda chains</td>
<td>- B ⇒ Bone lesions</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
<td><strong>2 major criteria</strong></td>
</tr>
<tr>
<td>1. Bone marrow infiltration with 10-30% plasma cells</td>
<td><strong>1 major and 1 minor criteria</strong></td>
</tr>
<tr>
<td>2. Paraprotein less than level defined above</td>
<td><strong>3 minor criteria always including 1 and 2</strong></td>
</tr>
<tr>
<td>3. Lytic bone lesions</td>
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Various other entities constitute plasma cell dyscrasias including plasmacytomas and plasma cell leukaemia. Plasmacytoma is a localised tumour either in bone (solitary plasmacytoma of bone) or in tissues other than bone (extraosseous plasmacytoma). In order to establish this diagnosis, it is imperative to exclude the presence of any other lesions and also the presence of lymphoma. This condition is defined by the WHO as a plasma cell neoplasm characterised by the presence of either 20% or an absolute count of 2 x 10^9/L monoclonal plasma cells in the peripheral blood. These malignant cells can also be found in extramedullary tissues including solid organs like the liver or spleen, or fluids like pleural effusions, ascites or cerebrospinal fluid. This condition can be with the presenting feature or evidence of progression of multiple myeloma. Despite the fact that Waldenström's macroglobulinaemia is caused by malignant B-cell proliferation with production of IgM, it is no longer classified as part of the immunosuppressive disorders.

This is the first study, to the author's knowledge, that evaluates the clinical profile of patients diagnosed with immunosuppressive disorders, and relates it to the orthopaedic setting.

Materials and methods
Patient population
Serum protein electrophoresis (SPEP) was performed on a total of 582 patients from May 2005 to September 2008, at the Steve Biko Academic Hospital. All these patients were included in the study and the data available on these patients collected (Figure 1). A SPEP is a laboratory assay, used only to identify a monoclonal protein, usually within the setting of immunosuppressive disorders.  

![Figure 1: Outline of method in data collection](image)

Data collection
The following data were collected on all patients included in this study:

- Haematological parameters:
  - Haemoglobin level
  - Bone marrow aspirate and trephine biopsy results

- Biochemical parameters:
  - Serum creatinine levels
  - β2-microglobulin levels
  - Serum and urine electrophoresis data
  - Albumin level
  - Serum calcium levels (both corrected and ionised)

- Immunological parameters:
  - Immunoglobulin subfraction quantification

- Radiological parameters:
  - All radiological records available on patients, in an attempt to identify any lytic or sclerotic lesions and features suggestive of osteopetrosis

- Clinical information:
  - Reasons prompting the investigations were collected from the laboratory clinical data supplied by the clinicians on laboratory request forms.
Data analysis

The following parameters were assessed:
- Epidemiological features of patients fitting diagnostic criteria for any of the immunoscretory disorders
- Whether patients were adequately evaluated (i.e. all necessary investigations performed) to establish or exclude the diagnosis of an immunoscretory disorder
- Staging at time of diagnosis
- Patient follow-up in MGUS cases. As this is considered a precursor lesion, monitoring should be performed biannually.

Results

Patient population

In total, 131 patients were identified with various types of monoclonal plasma cell disorders (Figure 2). Of these, 39 (6.7%) had multiple myeloma (using the 2003 WHO criteria), including two cases of non-secretory multiple myeloma. In both these cases, the diagnosis was established on biopsy results of pathological fractures. Waldenström’s macroglobulinaemia was present in seven (1.2%) patients and 83 (14.3%) had a MGUS. The age range varied from 37 to 86 years (mean 59) in multiple myeloma and 15 to 89 years (mean 61) among patients with MGUS.

This group also included one case of plasma cell leukaemia and one case with a plasmacytoma. Of note is the fact that 17% (14 cases) of the patients classified as having a MGUS had lytic bone lesions. This finding excludes the diagnosis of MGUS.

Patient staging at time of diagnosis

Patient staging could only be determined using various staging systems. The vast majority of patients did not have sufficient parameters to determine staging using the Salmon Durie classification, but the International Staging System, however could be assessed. Of the patients staged, 42% were stage III, 55% stage II and only 3% stage I, with life expectancy estimated at 29, 44 and 62 months respectively. Reasons for this late presentation may be a low level of suspicion by clinicians, but also late presentation by patients.

MGUS diagnosis and follow-up

In total 83 patients with MGUS were identified, of whom 24 received a full diagnostic work-up confirming the diagnosis. In the remaining patients (59), a monoclonal protein was present, but these patients were not assessed to determine an abnormality in terms of CRAB, and a diagnosis of multiple myeloma could therefore not be made.

As MGUS is regarded as a premalignant condition, patients should be assessed 6 to 12 monthly in terms of M-protein size and clinical condition. Only 11% were followed up in our clinical setting.

Discussion

The diagnosis of multiple myeloma and associated malignancies can be fraught with difficulty. The recent change in diagnostic criteria was designed to simplify the diagnosis and to possibly establish the diagnosis earlier (Table I).

Patients can present with a vast array of clinical symptoms, ranging from non-specific symptoms like fatigue, recurrent infections and kidney failure to pathological fractures and bone pain. The most common presenting symptom in patients with MM is bone pain, noted in approximately 60% of cases, with up to 80% having radiological abnormalities.7 The degree of pain is usually mild to moderate, but can be severe and is typically present for between 6 to 12 months. Back and chest pain, and less frequently extremity pain, is exacerbated by movement, and is usually not present while sleeping.8 Pathological fractures may occur spontaneously or following minor trauma.7 For these reasons, many patients present primarily to the orthopaedic surgeon. Others symptoms include fatigue (secondary to anaemia),9 recurrent infection (due to immune paresis),9 renal insufficiency, neurological symptoms,9 hyperviscosity syndromes10 and bleeding tendencies.11

<table>
<thead>
<tr>
<th>Table II: Standard investigations as suggested by Kyle et al1</th>
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<tbody>
<tr>
<td><strong>Haematological investigations</strong></td>
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<tr>
<td>- Full blood count with differential counts</td>
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<td>- Bone marrow aspirate with trephine biopsy</td>
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<tr>
<td>- Immunophenotyping and immunohistochemistry</td>
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<td>- Conventional cytogenetics</td>
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<td>- Fluorescent in situ hybridisation (FISH)</td>
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<td><strong>Biochemical investigations</strong></td>
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<tr>
<td>- Lactate dehydrogenase levels</td>
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<tr>
<td>- Calcium levels</td>
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<tr>
<td>- Creatinine levels</td>
</tr>
<tr>
<td>- β2-microglobulin</td>
</tr>
<tr>
<td>- Routine urine analysis</td>
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<tr>
<td><strong>Proving monoclonality</strong></td>
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<tr>
<td>- Serum protein electrophoresis with immunofixation</td>
</tr>
<tr>
<td>with quantitation</td>
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<tr>
<td>- Free light chains</td>
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<tr>
<td>- Bence Jones protein analysis in urine</td>
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<tr>
<td>- Serum free light chain analysis</td>
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<tr>
<td><strong>Radiological examination</strong></td>
</tr>
<tr>
<td>- Skeletal survey including at least:</td>
</tr>
<tr>
<td>- Spine</td>
</tr>
<tr>
<td>- Pelvis</td>
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<tr>
<td>- Skull</td>
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<td>- Humeri</td>
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<tr>
<td>- Femurs</td>
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</table>
Due to the complex diagnosis which can present with a vast array of symptoms, Kyle and co-workers suggested a range of special investigations which should be undertaken to exclude the diagnosis (Table II). These can be performed by the attending physician or on a reference basis. It is important to remember that no single assay or investigation in isolation is considered sufficiently specific to exclude the diagnosis. An example is the two cases of non-secretory multiple myeloma, as these patients did not have M proteins on the serum protein electrophoresis.

The radiographic appearance is classically referred to as ‘punched-out’ lytic lesions (Figure 3), and often expansile bone lesions. Of critical concern is the fact that osteopaenia may be the only presenting radiological feature. Despite the fact that classical radiological findings are often associated with a diagnosis of myelomatosis, interpretation of single X-rays in isolation is not advised as it cannot be considered diagnostic. If the diagnosis of myeloma is considered, it is advisable that a full skeletal survey should be conducted together with a range of other special investigations (as outlined in Table II), in collaboration with a multidisciplinary team.

As a large proportion of these patients can present primarily to the orthopaedic surgeon, the role of the orthopaedic surgeon in the management entails a high index of suspicion with appropriate investigation and referral. Impending and complete fractures should be surgically stabilised and irradiated. Irradiation can also be used for palliation of pain and treatment of neurological symptoms. Of note, surgery in this population group is likely to be complicated as the gammopathy may compromise organ function, presenting as renal dysfunction, coagulopathies, etc.

**Figure 3: Radiological findings can vary from a diffuse mottled appearance (illustrated above) to the classic punched-out appearance**

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**If the diagnosis of myeloma is considered, it is advisable that a full skeletal survey should be conducted together with a range of other special investigations**

When a patient does not fulfill the criteria for a plasma cell malignancy, a diagnosis of monoclonal gammopathy of undetermined significance should be considered. This M-protein may regress, remain stable, or progress to overt malignant disease. For this reason, all patients found to have MGUS (ensuring that myelomatosis is not present) should be followed up on a 6 to 12 monthly interval.

In conclusion, multiple myeloma is an important medical condition, often presenting to the orthopaedic surgeon for diagnosis and/or surgical management. It is therefore of the utmost importance that every orthopaedic surgeon has a high index of suspicion and a clear diagnostic approach to these patients.

*This article is the sole work of the authors. No benefits of any form have been received from a commercial party related directly or indirectly to the subject of this article although a grant has been applied for.*

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