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ENDGAMES

PICTURE QUIZ

Increasing confusion in a man after a fall—just a head injury?

K Birdi *specialty trainee in radiology*, J Weir-McCall *specialty trainee in radiology*, R Grace *consultant haematologist*, D C Howlett *consultant radiologist*

Eastbourne District General Hospital, Kings Drive, Eastbourne BN21 2UD, UK

A 79 year old man presented with his carer to the accident and emergency department with a recent history of generalised weakness, tiredness, and weight loss. According to his carer, the patient had been having generalised aches and pains and had become increasingly irritable and confused after a head injury during a recent fall.

On examination, his Glasgow coma scale score was 13 and he was mildly disoriented in time and place. Soft tissue swelling was noted over his forehead, which was consistent with his fall. His neurological, cardiovascular, and respiratory examinations were unremarkable. Blood tests showed a haemoglobin concentration of 98 g/L (reference range 130-180), mean cell volume 87 fl (82-100), urea 10.9 mmol/L (2.5-7.5), creatinine 172 μmol/L (46-92), calcium 3.32 mmol/L (2.1-2.55), total protein 120 g/L (63-82), albumin 22 g/L (35-50), white cell count 3.9×10^9/L (4-11), neutrophil count 2.4×10^9/L (2-7.5), and erythrocyte sedimentation rate 98 mm in the first hour (<10).

In view of his altered consciousness level and history of head injury, he was referred for a cranial computed tomography, which showed age related involutional change and no acute intracranial haemorrhage. However, lucent areas were identified in the skull vault and a lateral skull radiograph was performed for further evaluation (fig 1).

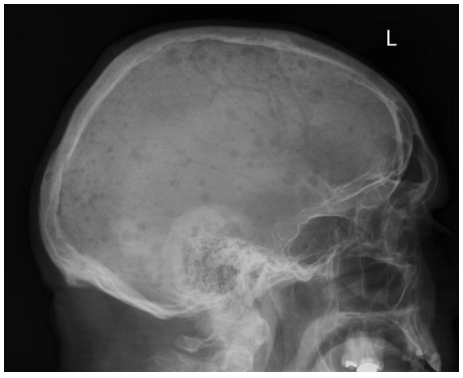

Fig 1 Lateral skull radiograph

Questions

1 What are the radiographic findings?

2 Given the patient's history, blood results, and radiographic findings, what is the most likely diagnosis?

3 What further investigations would you request and why?

4 What is the management of this condition?

Answers

1 What are the radiographic findings?

Short answer

The skull radiograph shows the typical appearance of a "pepper pot" skull, characterised by numerous well defined "punched out" lytic lesions.

Long answer

Multiple well defined osteolytic lesions of varying sizes throughout the skull vault giving it a "pepper pot" appearance (fig 2).[1]

Correspondence to: kbirdi@doctors.org.uk

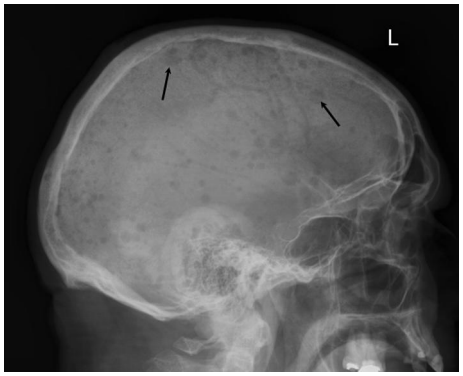

Fig 2 Lateral skull radiograph showing multiple well defined osteolytic lesions of varying sizes throughout the skull vault (arrows)

2 Given the patient's history, blood results, and radiographic findings, what is the most likely diagnosis?

Short answer

Multiple myeloma.

Long answer

Multiple myeloma is a haematological malignancy characterised by an excess of plasma cells in the bone marrow, monoclonal protein, osteolytic bone lesions, renal disease, immunodeficiency, and hypercalcaemia.[2]

It has an incidence of 50 cases per million per year in the United Kingdom. The median age at presentation is 70 years, with fewer than 2% of patients presenting below the age of 40 years. It is more common in men and twice as common in black people as in white people.[2 3]

The cause of multiple myeloma is unclear. The pathophysiological effects are caused by the interaction of the myeloma cells with bone marrow cells and the effects of the cytokines and immunoglobulins that they secrete.[2 3] IgG is the most common paraprotein produced (60%), followed by IgA (20%) and IgD (2%). IgE and IgM myelomas are rare. In addition, free immunoglobulin light chains of the κ or λ type are produced in 20% of cases and filtered by the kidneys. In 1-2% of patients, monoclonal protein is not present in the serum or urine (non-secretory myeloma). Normal polyclonal immunoglobulin production is reduced (immunoparesis) in 80% of patients at presentation.

Myeloma cells typically replace the normal bone marrow of the axial skeleton and proximal long bones.[2 3] They produce numerous cytokines, especially interleukin 6, which cause severe demineralisation and bone destruction (fig 2) by inhibiting new bone formation by osteoblasts and stimulating osteoclast activity.

Various patterns of multiple myeloma are recognised according to the location of the bone lesions and plain film radiographic appearances.[1]

Disseminated multiple myeloma predominantly affects the axial skeleton in the following distribution: vertebrae > ribs > skull > shoulder > pelvis > long bones. It is characterised by numerous well defined punched out osteolytic lesions and endosteal scalloping. These lesions give the typical pepper pot appearance to the skull on radiography. There may be generalised osteopenia of the spine, with associated multiple compression fractures; diffuse osteolysis of the pelvis and sacrum; and expansile osteolytic lesions in the ribs, pelvis, and long bones.

A solitary plasmacytoma is a discrete soft tissue mass of plasma cells in the vertebral body or pelvis and can be considered as a singular counterpart of multiple myeloma. Early diagnosis of a solitary plasmacytoma can occasionally prevent development of or progression to multiple myeloma. Spinal plasma cell myeloma is characterised by sparing of the posterior elements, paraspinal soft tissue mass with extradural extension, and scalloping of the anterior margin of the vertebral bodies secondary to pressure from adjacent enlarged lymph nodes.

The sclerotic form of multiple myeloma is rare and is associated with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes).

Several genetic abnormalities in the myeloma plasma cells, such as deletions of chromosome 13, chromosome 17 deletions, and translocations involving the immunoglobulin heavy chain gene on chromosome 14, have been implicated in the pathogenesis of the disease. Generally, gene mutations presage an adverse outcome.[4]

3 What further investigations would you request and why?

Short answer

Serum electrophoresis will detect paraproteins in the blood as a band of monoclonal immunoglobulins. Urine electrophoresis will check for free light chains (Bence-Jones proteins) in the urine. Immunofixation will establish the immunoglobulin subtype in the blood and the subtype of light chain in the urine. Bone marrow aspiration and biopsy will confirm the degree of marrow infiltration and presence of malignant plasma cells by immunohistochemistry. Serum immunoglobulin concentrations are typically reduced. A radiological skeletal survey is necessary to screen for osteolytic lesions.

Long answer

The diagnosis of multiple myeloma is established by bone marrow aspiration and biopsy, which will confirm the extent of marrow infiltration and the presence of clonal plasma cells by immunohistochemistry.[3 5 6] Immunofixation of serum and urine will confirm the subtype of immunoglobulin (IgG, IgA, IgM, IgD, or IgE) in the blood and the subtype of light chain (κ or λ) in the urine.

Serum electrophoresis will check for the presence of paraprotein in the blood, whereas urine electrophoresis will detect the presence of light chains (Bence-Jones protein) in the urine. Serum immunoglobulin concentrations are typically reduced in the disease, except for the immunoglobulin subtype produced by the myeloma cells. A skeletal bone survey (radiographs of the skull, spine, pelvis, chest, humeruses, and femurs) is necessary to screen for osteolytic lesions.[3 5 6]

Additional tests are performed to estimate tumour burden and prognosis. These include bone marrow cytogenetics; fluorescent in situ hybridisation (FISH); cross sectional imaging with computed tomography or magnetic resonance imaging; and measurement of plasma viscosity, serum paraproteins, creatinine clearance, albumin, β2 microglobulin, and urinary light chains.[3 5 6]

The results of any single test are not enough to make a diagnosis of multiple myeloma. Diagnosis is based on a combination of factors, and in 2003 the International Myeloma Working Group established diagnostic criteria for asymptomatic myeloma, symptomatic myeloma, and monoclonal gammopathy of undetermined significance.[5] These criteria were subsequently updated in 2009 (box).[6]

Diagnostic criteria for the different forms of myeloma

Symptomatic myeloma

Clonal bone marrow plasma cells ≥10% and

Presence of serum or urinary monoclonal protein (except in cases of true non-secretory myeloma) and

Evidence of myeloma related end organ damage ("CRAB" features):

- Calcium increase (serum calcium ≥2.75 mmol/L) or
- Renal insufficiency (serum creatinine >173 mmol/l)
- Anaemia (with a haemoglobin <100 g/L)
- Bone lesions (lytic lesions, severe osteopenia, or pathological fractures)

Asymptomatic myeloma

Serum monoclonal protein (IgG or IgA) ≥30 g/L or clonal bone marrow plasma cells ≥10% (or both) and

Absence of myeloma related end organ damage

Monoclonal gammopathy of undetermined significance

Clonal bone marrow plasma cells ≥10% and

Serum monoclonal protein <30 g/L and

Clonal bone marrow plasma cells <10% and

Absence of myeloma related end organ damage

4 What is the management of this condition?

Short answer

Initial management is with intravenous fluids (3 L/day), intravenous bisphosphonate to treat hypercalcaemia, and consideration of urgent dexamethasone to prevent further renal damage by light chains. Younger fitter patients are treated with high dose chemotherapy before stem cell transplantation. Older and less fit patients are treated with less intensive regimens, which now incorporate thalidomide to improve response. Supportive measures include treatment with analgesia and palliative radiotherapy to help improve bone pain and reduce fracture rates. Blood transfusion and erythropoietin injections are used to correct anaemia. Patients in acute renal failure may be dialysed. Acute infections are treated with appropriate antibiotics, and regular immunoglobulin infusions may be needed in recurrent infections.

Long answer

Treatment is recommended for symptomatic myeloma and includes initial treatment, chemotherapy, and supportive care.

Initial resuscitation is with intravenous fluids (3 L/day), intravenous bisphosphonate to treat hypercalcaemia, and consideration of urgent dexamethasone to prevent further renal damage by light chains.[2 3]

Chemotherapy usually achieves a remission of 12-18 months followed by relapse, which then requires further treatment to induce remission.[2 3] In the UK, young fit patients (≤65 years) are treated with chemotherapy to reduce disease bulk, typically with CTD (cyclophosphamide, thalidomide, and dexamethasone), followed by autologous stem cell transplantation. Older and less fit patients are treated with combinations of less intensive chemotherapy to help minimise the side effects of high dose chemotherapy. Thalidomide is now added to many combinations of chemotherapy because it has been shown to improve their effectiveness.[2] However, thalidomide and other immunomodulatory drugs are associated with an increased risk of thrombosis and a risk management policy is in place to minimise adverse events. In other European countries (not the UK), bortezimib based chemotherapy regimens are used for elderly patients who are not eligible for a transplant.

About a quarter of myeloma patients are unresponsive to chemotherapy. This is probably because of refractory disease and its inherent resistance to treatment.[2 3] Those who are resistant or who relapse are treated with new agents, such as bortezimib, to which they have not yet been exposed.

Several supportive care measures are available for symptomatic patients.[3] Bone pain is treated with analgesia and bisphosphonates, which also help to reduce fracture rates. Palliative radiotherapy will help to improve bone pain in localised disease. Bone pain caused by vertebral compression fractures may be reduced with percutaneous injections of polymethylmethacrylate into the affected vertebral bodies using vertebroplasty or kyphoplasty techniques. Neuropathic pain secondary to nerve root compression or chemotherapy agents, such as thalidomide or bortezomib, may be treated with gabapentin or amitriptyline.

Acute infections are treated promptly with broad spectrum intravenous antibiotics until culture results are known. Regular immunoglobulin infusions may be needed in recurrent infections. Affected patients should also be vaccinated against influenza, Streptococcus pneumoniae, Neisseria meningitides, and Haemophilus influenzae.

Blood transfusion and erythropoietin injections are used to correct anaemia.

Patients with renal failure are encouraged to drink at least 3 L a day to prevent renal impairment or are dialysed if they are in acute renal failure.

Patient outcome

Unfortunately, the patient's condition deteriorated and, despite adequate treatment, he died from complications of the disease.

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Patient consent not required (patient anonymised, dead, or hypothetical).

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