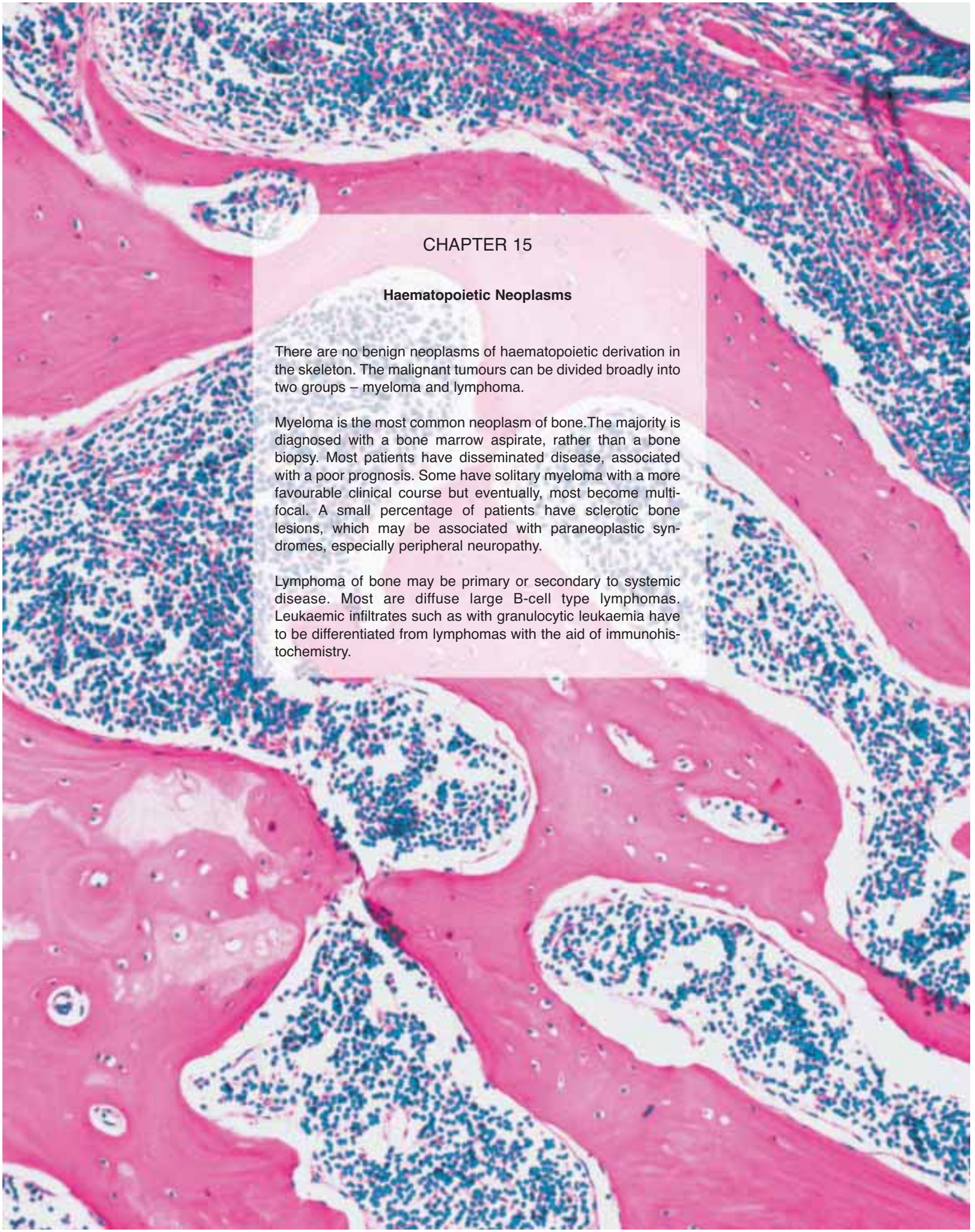

CHAPTER 15

Haematopoietic Neoplasms

There are no benign neoplasms of haematopoietic derivation in the skeleton. The malignant tumours can be divided broadly into two groups – myeloma and lymphoma.

Myeloma is the most common neoplasm of bone.The majority is diagnosed with a bone marrow aspirate, rather than a bone biopsy. Most patients have disseminated disease, associated with a poor prognosis. Some have solitary myeloma with a more favourable clinical course but eventually, most become multi-focal. A small percentage of patients have sclerotic bone lesions, which may be associated with paraneoplastic syn-dromes, especially peripheral neuropathy.

Lymphoma of bone may be primary or secondary to systemic disease. Most are diffuse large B-cell type lymphomas. Leukaemic infiltrates such as with granulocytic leukaemia have to be differentiated from lymphomas with the aid of immunohis-tochemistry.

Plasma cell myeloma

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Definition

Plasma cell myeloma is a monoclonal neoplastic proliferation of plasma cells of bone-marrow derivation, usually multicentric, that eventually infiltrates various organs but rarely produces plasma cell leukaemia. It is characterized by osteolytic lesions, bone pain, hypercalcemia, a monoclonal gammopathy, and disorders due to depositon of abnormal immunoglobulin chains (amyloid) in various tissues, including kidney.

ICD-O code 9732/3

Synonyms and variants

Myeloma, multiple myeloma.
The following variants of plasma cell myeloma have been described {844}: non-secretory myeloma, indolent myeloma , smoldering myeloma, plasma–cell leukaemia (PCL), in addition to extramedullary plasmacytoma, and solitary plasmacytoma of bone. The exact distinction is based on clinical and radiographic features.

Epidemiology

Plasma cell myeloma is the most frequent tumour that occurs primarily in bone and the most common lymphoid neoplasm in Blacks and the second most common in Whites. It is rare in individuals younger than 40 years (less than 10%). Most patients are in the sixth and seven decades of life. The median age at diagnosis is 68 years in males and 70 in females. Both sexes are equally affected {512}.

Sites of involvement

The bones that contain haematologic marrow in adults are the most frequently involved: vertebrae, ribs, skull, pelvis, femur, clavicle and scapula {843,1850}.

Clinical features / Imaging

The extensive osteolytic skeletal lesions cause bone pain, pathological fractures, hypercalcemia and anaemia. The lumbar or thoracic spinal regions are most often affected by pain. Frequently a pathological fracture is the first symptom. Most fractures affect the spine. Neurologic symptoms due to spinal cord or nerve roots lesions, secondary to extraosseous extension of the tumour or pathological fracture, are frequently observed. Peripheral neuropathy is increasingly observed with the osteosclerotic variant of multiple myeloma but it is rare with classic plasma cell myeloma {2155}. Anaemia is a consequence of marrow destruction and renal damage with resultant loss of erythropoetin {122}. An M-component is found in the serum or urine in 99% of the patients. The monoclonal proteins are in 50% of the cases of the IgG class, 25-20% of the IgA class, and, rarely, of the IgM, IgD or IgE classes. Biclonal gammopathies are found in 1% and a monoclonal light chain (Bence-Jones protein) is found in the serum in 75% of the patients {1850}. Renal failure is the result of tubular lesions due to monoclonal light chain

Table 15.01
Diagnostic criteria for plasma cell myeloma.

Major criteria:
> Plasmacytoma on biopsy > Marrow plasmacytosis (>30%) > M component: Serum IgG>3.5g/dl, IgA>2g/dl Urine ->Ig/24 hr or kappa or lambda (Bence Jones protein) without amyloidosis
Minor criteria:
> Marrow plasmacytosis (10-30%) > M component present but less than listed above > Lytic bone lesions > Reduced normal levels of immunoglobulins (<50% normal: IgG <600mg/dl, IgA<100 mg/dl, IgM<50mg/dl)
The diagnosis of myeloma requires a minimum of one major and one minor criterion or three minor criteria, which must include the first two. These criteria must be present in a clinical setting of symptomatic and progressive disease.

From references {843,1850}.

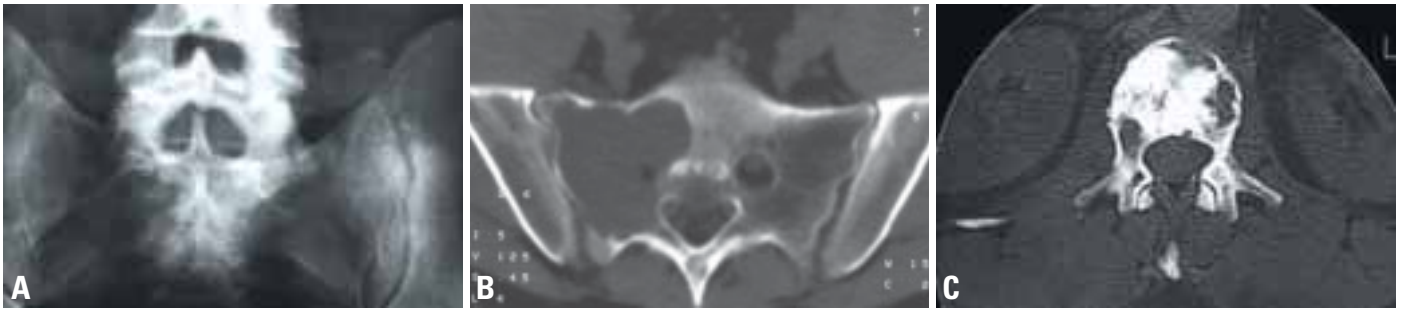

Fig. 15.01 Plasma cell myeloma. **A** Plain radiograph of the lumbo-sacral region of the spine shows a very light radiolucency of the right wing of the sacrum. **B** CT scan of the same patient, at the level of S2, shows loss of the cancellous bone of the right wing of the sacrum, of a large area of the vertebral body, and small scalloping of the endosteal surface of the cortical bone. **C** Patient with POEMS syndrome with multiple lesions in the skeleton. CT scan of L1 with extensive radiodense areas, and points of disruption in the anterior cortex.

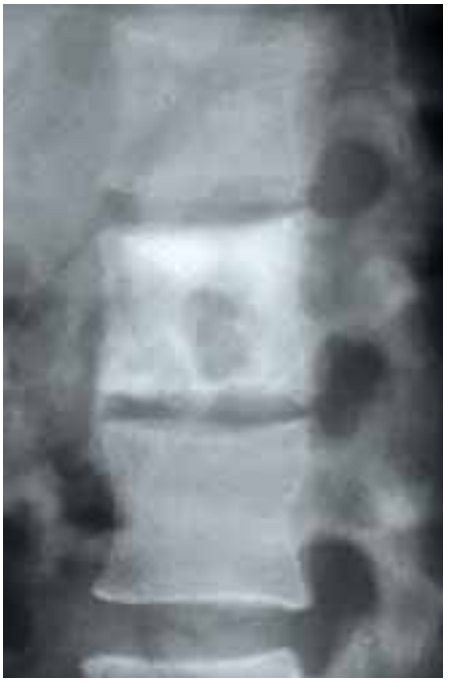

Fig. 15.02 Plasma cell myeloma. Patient with POEMS syndrome with multiple lesions in the skeleton. X-ray of the dorso-lumbar region of the spine showing marked radiodensity with a less radiodense central area. The discal space L1-L2 is typically diminished.

Fig. 15.03 Plasma cell myeloma. Photographs of gross autopsy specimens. The normal bone structure and bone marrow of the vertebral bodies are replaced by a gelatinous haemorrhagic tissue.

proteinuria. The patients have often recurrent bacterial infections, partially because a decreased normal immunoglobulin production due to displacement by the neoplastic clone.

The myelomatous bone lesions are lytic, sharply demarcated lesions, being the consequence of replacement of bone trabeculae by tumour tissue, are not surrounded by a sclerotic zone and may reach 5 cm in its greatest diameter. Erosions of the cortex are commonly observed but prominent periosteal new bone formation is not. Expansion of the affected bone may occur in bones with a small diameter, such as the ribs. The earliest and more severe changes are seen in the skull, vertebrae, ribs and pelvis. About 12-25% of patients have no detectable foci of bone destruction at presentation but may show generalised osteoporosis {2155}. Solitary myeloma lesions are also typically lytic and may also expand the bone. Infrequently the lesions in plasma cell myeloma may be sclerotic, which are typical for the very rare POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes) {122, 871}. CT and MRI studies may discover a very subtle small lesion not visible on plain radiographs. The features of MRI are variable, because plasma cell myeloma does not involve the marrow in a homogeneous fashion and because the extent of fatty marrow replacement which varies with age. For differential diagnosis metastatic carcinoma, malignant lymphoma, and hyperparathyroidism have to be considered. The lesions of metastatic carcinoma and malignant lymphoma are usually positive on bone scan, whereas those of myeloma are usually not {538}.

Aetiology

The aetiology is largely unknown. Possible, but unproven, aetiologic factors include long standing chronic infections (chronic osteomyelitis, rheumatoid arthritis, etc.), exposure to low level radiation (radiologists, nuclear plant workers), and exposure to asbestos, pesticides, petroleum products, rubber, plastic and wood products {1851}. Some cases of POEMS syndrome have been associated with Kaposi sarcoma / human herpesvirus 8 infection {154,1467}.

Macroscopy

Biopsy or curettage samples show fragments of tan-grey soft tissue. At autopsy, soft pink or grey friable masses are the

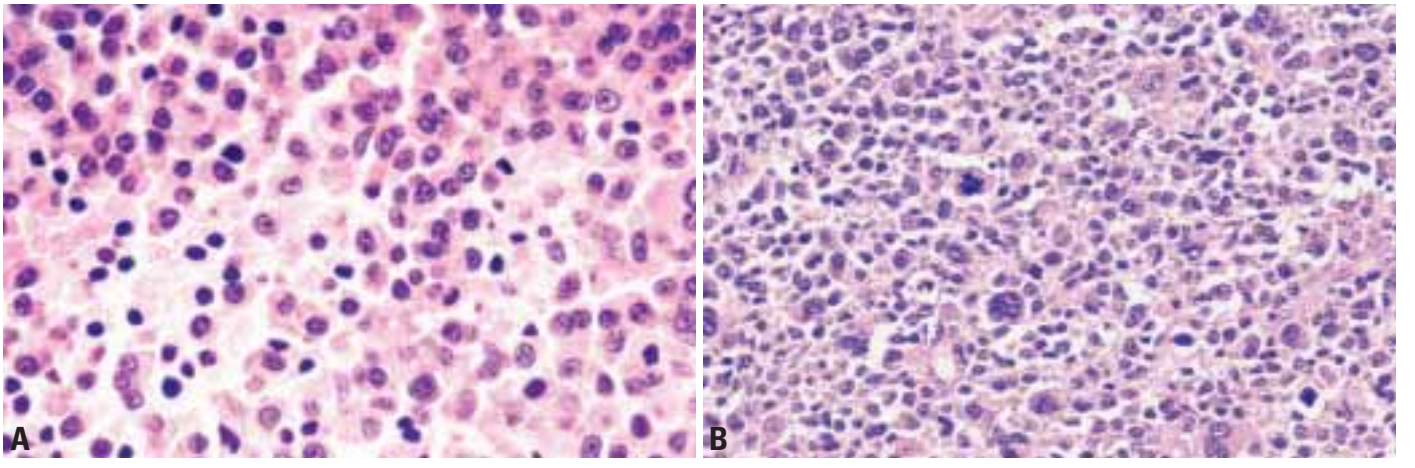

Fig. 15.04 Plasma cell myeloma. **A** High power view shows cells with eccentric round or oval nuclei, with a speckled chromatin and abundant cytoplasm, that in the tissue section stains pink. **B** Poorly differentiated plasma cell myeloma, showing cellular pleomorphism with frequent multinucleated cells and atypical mito-tic features, consistent with the term "anaplastic myeloma".

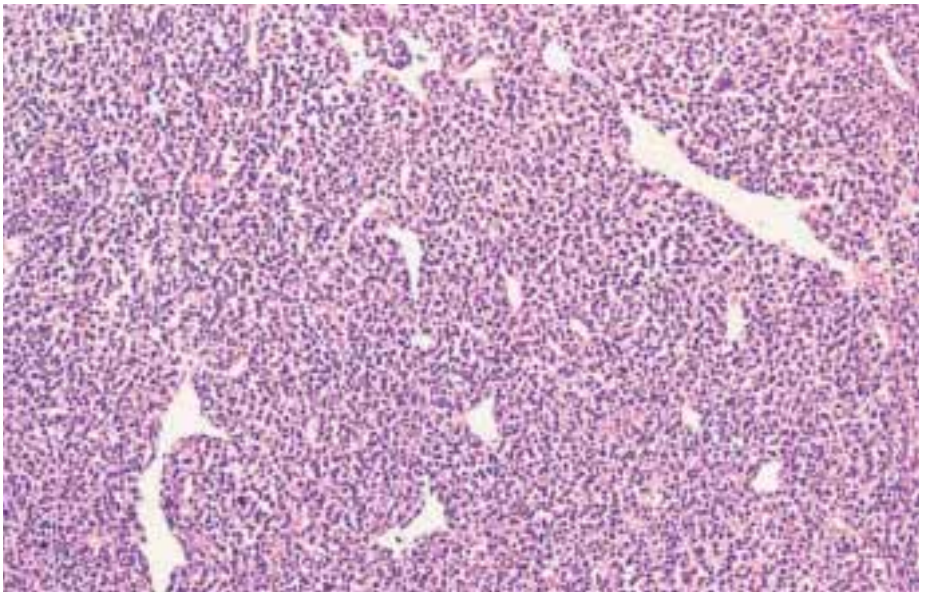

Fig. 15.05 Plasma cell myeloma. Low power appearance shows a rich vascular pattern. The tumour cells surround the vascular channels, simulating a haemangiopericytomatous pattern.

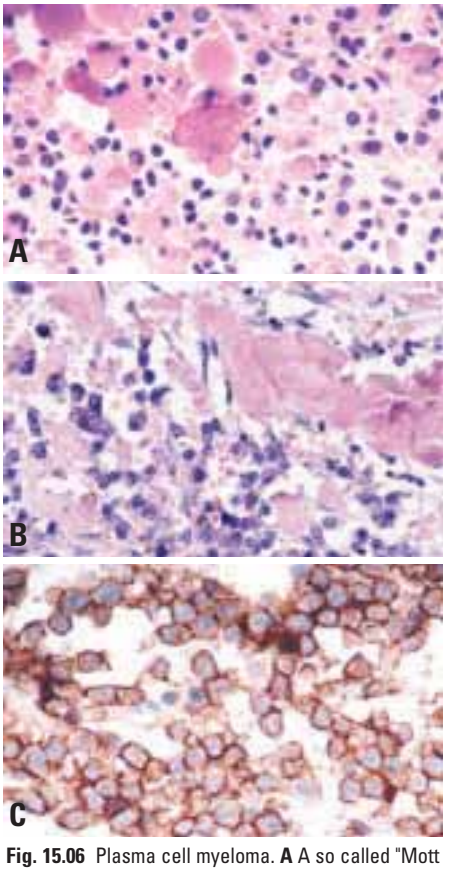

Fig. 15.06 Plasma cell myeloma. **A** A so called "Mott cell" is shown in the centre of the picture, with grape-like cytoplasmic inclusions. The cell is surrounded by numerous Russell bodies. **B** Plasma cell myeloma containing amyloid. Deposition of pale, waxy amorphous proteinaceous material in between neoplastic plasma cells (Congo red stain). **C** Immunoexpression of CD 138 in almost all neoplastic cells.

typical appearance. Diffuse involvement of bone marrow and discrete nodules are also common. Some plasma cell myelomas may simulate a lymphoma showing a fish-flesh appearance. It is quite common to see expansion of the affected bone and extraossous extension, collapse of one or several vertebral bodies and pathological fractures. Very infrequently the tumour masses have a grey, waxy appearance due to extensive amyloid deposition. Unusual cases have a combination of lytic and sclerotic changes.

Histopathology

Plasma cell myeloma is a neoplasm of round or oval cells of the plasma cell lineage showing a spectrum of variable features of cellular maturity that have prognostic significance. Well differentiated tumours show sheets of closely packed cells, that resemble normal plasma cells, with little intercellular matrix. In the histological sections these cells have abundant, dense eosinophilic cytoplasm and show distinct cell outlines. The nucleus is eccentric, with the chromatin clustered at the periphery, often showing a cartwheel appearance and a prominent nucleolus. Mitotic figures are rare in well differentiated plasma cell myeloma The cytological features are better observed in Giemsa stained preparations in which the cytoplasm is basophilic with a perinuclear clear zone that correspond ultrastructurally to a well developed RER and a prominent Golgi centre, respectively. The tumour cells may accumulate immuno-globulins in the cytoplasm and show a morular appearance or "Mott cells". Extracellular globules of polymerized immunoglobulines, called Russell bodies, may be also observed. The cells of less differentiated tumours show nuclei with less clumping of the chromatin and enlarged nucleoli, and the cytoplasmic membrane becomes indistinct. The poorly differentiated plasma cell myeloma may show atypical cells, with occasional double nuclei, brisk mitotic activity and atypical mitotic figures making difficult to recognize the plasma cell nature of the cells.

Immunophenotype

Myeloma cells have the same features as normal plasma cells and express their own distinct antigen [plasma cell associated antigen (PCA, CD38)] {1270}. Plasma cell myeloma characteristically expreses monotypic cytoplasmic Ig and lacks surface Ig. In about 85% both heavy and light chains are produced, but in the remaining cases light chain only is expressed (Bence–Jones myeloma) {1178}. The monotypic expression of kappa or lambda immunoglobulin by the tumour cells establishes the diagnosis of malignancy {2169}. Myeloma cells frequently express the natural killer antigen CD56/58 which is not expressed in reactive plasma cells {405}. The majority of myelomas lack the pan-B antigens CD19 and CD20, while CD38 and the Ig-associated antigen CD79a are expressed in most cases {1270}, and CD138 {498} is a reliable marker for identifying and quantifying normal and tumoural plasma cells in paraffin sections. Myeloma cells may be positive for EMA {841}. Few cases may express CD10 {842} and occasionally plasma cell myeloma may show aberrant expression of myelomonocytic antigen {123}.

Prognostic factors

Multiple myeloma is generally an incurable disease (median survival 3 years; 10% survival at 10 years {560,1850}. A shorter survival time is associated with a higher stage {133,561}, renal insufficiency {133,561}, degree of marrow

replacement by tumour cells {1154}, cellular immaturity and atypia {1851}, high Ki-67 proliferation antigen levels {842} and chromosome deletion of 13q14 and 17p13 {1682}. The lack or weak expression of CD56 delineates a special subset of plasma cell myeloma at diagnosis with a lower osteolytic potential and a trend to develop a PCL {138}. The prognosis is better in solitary lesions.

Table 15.02
Diagnostic criteria of solitary myeloma (plasmacytoma of bone).

Diagnostic criteria
> A single tumour in the bone marrow showing identical macroscopic, microscopic, immunophenotype and genetic features to those of plasma cell myeloma > Solitary osteolytic lesion on radiological studies > Absence of other lesions on complete skeletal radiographs > No evidence of plasmacytosis in the bone marrow away of the solitary lesion

From references {137,719,834,1194,1260,1391}.

Malignant lymphoma

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P.C.W. Hogendoorn

Definition
Malignant lymphoma is a neoplasm composed of malignant lymphoid cells, producing a tumefactive lesion within bone.

ICD-O code 9590/3

Synonyms
Reticulum cell sarcoma, primary non-Hodgkin lymphoma of bone, Hodgkin lymphoma.

Epidemiology
Malignant lymphoma involving bone is unusual, accounting for approximately 7% of all bone malignancies. Lymphomas involving bone account for about 5% of extranodal lymphoma. Radiographic studies {249} show that 16% of patients with lymphoma have evidence of bone involvement. Patients may be of any age group but there is a tendency to involve adults, especially older adults. There is a male predominance {943}.

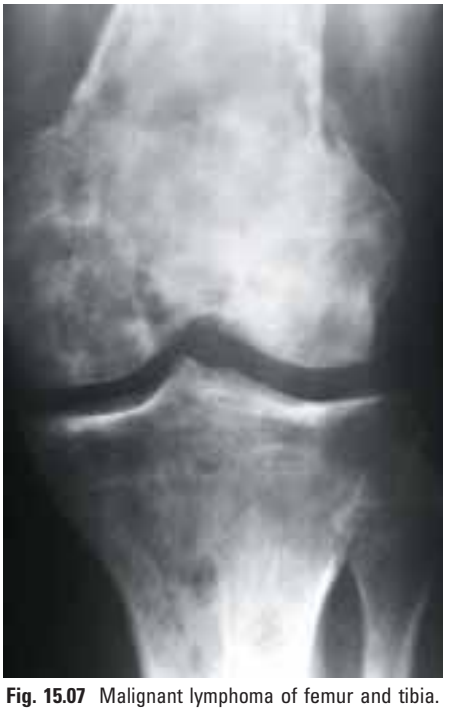

Fig. 15.07 Malignant lymphoma of femur and tibia. Note extensive lytic and sclerotic lesions.

Sites of involvement
Lymphoma affects portions of bone with persistent red marrow. The femur is the most commonly involved single site. The spine and the pelvic bones are other common sites. It is extremely unusual to see malignant lymphoma involving the small bones of the hands and feet. When malignant lymphoma presents in the spine or in the maxillary antrum, it is often difficult to know whether the process is primary in bone or in soft tissues.

Clinical features / Imaging
The majority of patients with lymphoma present with bone pain. Some patients present with a palpable mass. Neurological symptoms are common with involvement of the spine. Patients with primary lymphoma of bone rarely present with systemic or B symptoms, such as fever or night sweats. Occasionally, symptoms associated with hypercalcemia, such as constipation, lethargy and somnolence may be present {1512}. Lymphoma involving bone can be separated into four groups:
1) a single skeletal site, with or without regional lymph node involvement;
2) multiple bones are involved, but there is no visceral or lymph node involvement;
3) patients present with a bone tumour but work up shows involvement of other visceral sites or multiple lymph node at multiple sites;
4) the patient has a known lymphoma and a bone biopsy is done to rule out involvement of bone.
Groups 1 and 2 are considered primary lymphoma of bone.
The roentgenographic features are quite variable and somewhat non-specific. In the long bones, the diaphysis tends to be preferentially involved. The tumour tends to involve a large portion of the bone; it is not unusual to see destruction of up to half of the bone. Occasionally, the entire bone is destroyed. The process is poorly demarcated with a wide area of transition from normal bone. There may be variable sclerosis; rarely, the tumour is very sclerotic or entirely lytic. More commonly, however, it is a mixture of lysis and sclerosis. The cortex is frequently destroyed and there is a large soft tissue mass. In a flat bone, such as the pelvis, large areas of destruction with soft tissue extension on either side suggest a diagnosis of lymphoma. Periosteal new bone formation is unusual. A purely sclerotic lesion may be mistaken for Paget disease. If the cortex is not involved, the marrow destruction may not be obvious on plain roentgenograms. Radionuclide bone scan is almost always positive. Magnetic resonance images show signal abnormalities in the marrow,

Fig. 15.08 Malignant lymphoma in a 15-year-old boy. **A** Plain roentgenogram does not reveal the lesion. **B** MRI of the same case shows multifocal involvement of bone with signal changes.

whereas the plain roentgenograms may be completely normal.

Macroscopy

It is unusual to see gross specimens of malignant lymphoma involving bone, because the treatment is usually with radiation and/or chemotherapy, following diagnoses made with needle biopsies. However, a portion of bone may be resected if the patient presents with a pathological fracture. Grossly, a large portion of bone is involved, with cortical destruction. The lesion has the soft fish-flesh appearance of lymphoma elsewhere in the body.

Histopathology

The majority of lymphomas involving the skeleton show a diffuse growth pattern. Although bone marrow involvement is not uncommon in follicular small cleaved cell lymphoma, it is unusual to have this type of lymphoma present as a destructive bone tumour. Similarly, chronic lymphocytic leukaemia rarely presents as a tumefactive process. Consequently, most skeletal lymphomas are diffuse large cell type. It has a very characteristic growth pattern similar to involvement elsewhere, and tends to leave behind normal structures, such as medullary bone and marrow fat cells and permeate between these structures. The bony trabeculae may appear normal or may appear thickened or irregular, even pagetoid. 92% of primary non-Hodgkin lymphoma of bone was found to be of the large B cell type and only 3% diffuse follicle centre cell, 3% anaplastic large cell and 2% immunocytoma {943}. The cytological features of the large B-cell type show quite a bit of variation including marked multilobation {1703}. The nuclei tend to be large and irregular with a cleaved appearance. There frequently is a mixture of small, medium and large cells, giving rise to a polymorphic appearance. Nucleoli may be prominent. The cytoplasm is not abundant but may be amphophilic. Fine reticulin fibres are present between individual tumour cells. Occasionally, this gives rise to thick, fibrous bands. Rarely a lymphoma will have so much fibrosis that the tumour cells may spindle, even showing a storiform pattern, leading to an erroneous diagnosis of a sarcoma. Another common finding is associated infiltrate of non-neoplastic small lymphocytes. One problem with the diagnosis of lymphoma in bone is that the cells tend to get crushed. One may not be able to identify individual tumour cells but see complete replacement of the marrow with DNA smears. This may be associated with a very fine fibrosis. If a bone biopsy shows such crush artefact, a diagnosis of malignant lymphoma should be suspected.

Hodgkin lymphoma may involve the skeleton as a manifestation of widespread disease and produce a tumour mass but primary manifestations are

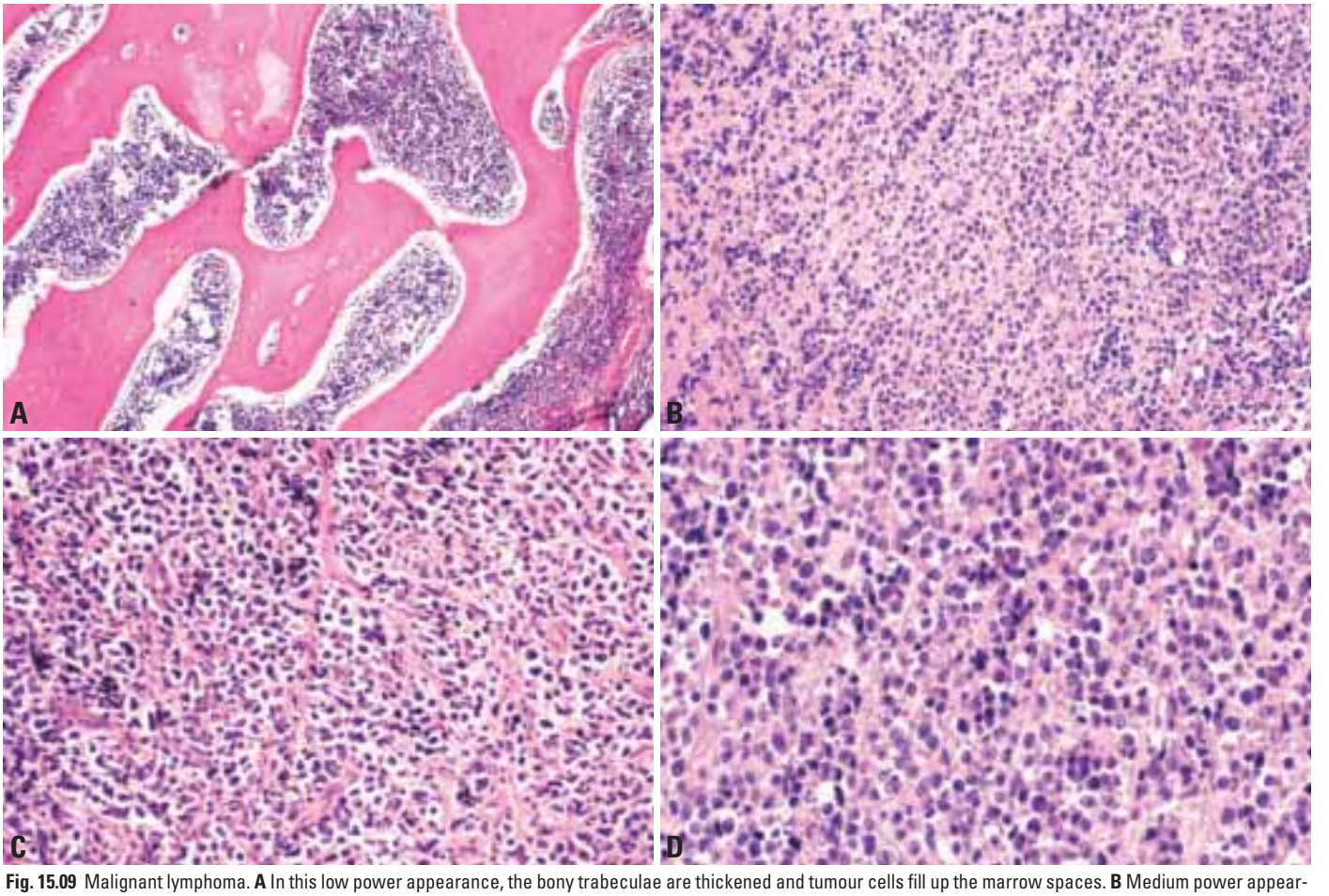

Fig. 15.09 Malignant lymphoma. **A** In this low power appearance, the bony trabeculae are thickened and tumour cells fill up the marrow spaces. **B** Medium power appearance of the neoplastic infiltrate. **C** In some cases lymphoma cells may cluster as shown in this photomicrograph. **D** Although nuclei are round and small there is more variation in size and shape of nuclei than is seen in Ewing sarcoma.

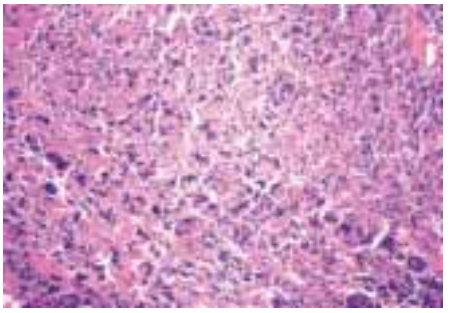

Fig. 15.10 Malignant lymphoma. Crush artefact is frequently present.

rare. Classical Reed-Sternberg cells with bi-lobed nuclei and prominent nucleoli are present but may be difficult to find. More commonly, one finds variants, such as large cells with large nuclei and prominent nucleoli. Variation in size and shape of the cells, especially the presence of plasma cells and eosinophils should alert one to the possibility of Hodgkin lymphoma. Areas of necrosis may be also prominent. Nodular sclerosing Hodgkin lymphoma and mixed cellularity are the usual types {1623}.

Leukaemic infiltrates may produce a tumour mass centred in bone. Patients with chronic or acute myelogenous leukaemia may present with destructive lesions of bone or granulocytic sarcoma {1390}. The clinical course may be indolent {2247}. Histological features of the infiltrating cells recapitulate the features of the systemic disease.

Immunophenotype

Immunoperoxidase stains have become indispensable in the recognition and subclassification of malignant lymphoma. Lymphomas involving bone are usually worked up in the same way as lymph node counterparts. Almost all primary lymphomas involving bone are B-cell neoplasms and hence stain with CD20 {943}. T-cell lymphomas and anaplastic large lymphomas are vanishingly rare. CD15 and CD30 stains recognize Reed-Sternberg cells of Hodgkin disease and myeloperoxidase reactions help support a diagnosis of granulocytic sarcoma.

Genetics

Specific studies on primary lymphomas of bone are lacking.

Prognostic factors

Although the prognosis of lymphoma has been reportedly associated with cell type {544} the most important prognostic indicator is the stage of the disease. Patients with the first two stages do remarkably well, whereas patients with stage 3 and stage 4 disease fare poorly {1626}. Recent data on primary non-Hodgkin lymphoma of bone show a 5-year overall survival of 61%, and 46% of patients progression free at 5 years, notwithstanding heterogeneous treatment in that series {943}. Patients at presentation older than 60 years have a worse overall survival and a worse progression-free period. Patients with the immunoblastic subtype have a worse survival than the centroblastic mono / polymorphic subtype or the centroblastic multilobated subtype. Tumour localization is not found to be a significant prognostic factor. According to the Ann Arbor classification there is no difference in survival between stage I and stage II tumours and just a trend towards worse prognosis in stage IV tumours {943}.