7 Plasma Cell Proliferations

7.1 Plasma Cell Myeloma/Bone Marrow Plasmacytoma (ICD-O: 9732/3)

Synonyms

- KIEL: Plasmacytic lymphoma (plasmacytoma)
- REAL: Plasmacytoma /plasma cell myeloma
- WHO: Plasma cell myeloma
- Other: Multiple myeloma, Kahler's disease

Definition

This neoplastic proliferation consists of a unique diagnostic triad of osteolytic bone lesions, marrow infiltration by atypical plasma cells, and serum monoclonal gammopathy (Kyle 1992; Schajowicz 1994; Malpas et al. 1995; Grogan et al. 2001).

Morphology

Macroscopy. The neoplasia is responsible for the development of nodules in the bone marrow that consist of soft grayish or yellowish homogeneous tissue and measure about 1 cm in diameter. These nodules transform into large polycyclic masses that destroy not only the bone architecture of the medulla but also the cortex with extension to the surrounding soft tissues. These bone lesions cause collapse of the vertebral bodies and fracture of tubular bones.

Histology. The diagnosis of plasma cell myeloma is based on the type of bone marrow infiltration, the quantity of neoplastic cells, and the morphology of the cells (Reed et al. 1981; Kyle 1992; Bartl et al. 1982, 1995; Sailer et al. 1995).

Early lesions are made up of small nests of neoplastic cells that are dispersed between adipose cells, more or less intermingled with hematopoietic cells, and at a distance from the arterioles (Fig. 7.1). This localized interstitial involvement can be difficult to diagnose. The presence of large plasma cells, blastic or pleomorphic variants, is useful in making the diagnosis.

The presence of aggregate of about 25 plasma cells (Grogan et al. 2001) as well as of more diffuse interstitial infiltrates (Fig. 7.2) favors the diagnosis of plasma cell myeloma. Some of the aggregate may develop along the bone trabeculae (Fig. 7.3).

In more advanced cases, sheets of plasma cells form nodules or strands destroying and replacing the hematopoietic tissue. Finally, densely packed plasma cells lead to massive involvement of the medullary spaces. Collagen bands can develop around vessels and bone trabeculae (Fig. 7.3). Destruction of bone trabeculae by osteoclastic hyperplasia is often observed, mostly in advanced disease.

The neoplastic cells exhibit a variety of morphologies that either predominate or are variably associated.

One of the most frequent neoplastic cell types is that of *mature plasma cells* (Fig. 7.1), Marschalko type; these cells have an eccentric nucleus with dense chromatin ("cartwheel" pattern), no or only one small nucleolus, a large ovoid or triangular basophilic cytoplasm, and a clear juxtanuclear halo (extremely large Golgi apparatus). Giant forms can be observed.

Another neoplastic cell type is *lymphoid plasma cells*. These are smaller than Marschalko type cells, with scanty cytoplasm surrounding a round nucleus with dense chromatin blocks. They seem to often be associated with IgD production (Reed et al. 1981).

Proplasma cells are larger, with a pale nucleus containing a central medium-sized nucleolus (Fig. 7.4). Other types of plasma cells have an irregular, "cleaved" or "notched" nucleus. Large cells with the morphology of *immunoblasts*, *plasmablasts* (Fig. 7.5), or even *giant multinucleated cells* mimicking Sternberg-Reed cells are also observed. Vacuoles may be located in the cyto-

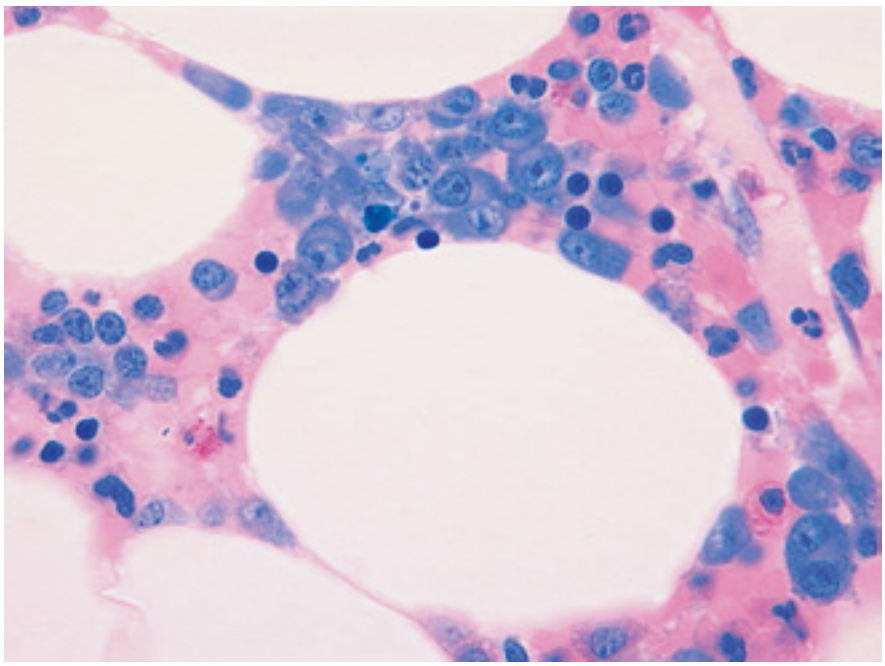

Fig. 7.1. Plasma cell myeloma. Early infiltration by dispersed small nests of mature plasma cells (Marschalko type), at a distance from capillaries and arterioles (Giemsa stain)

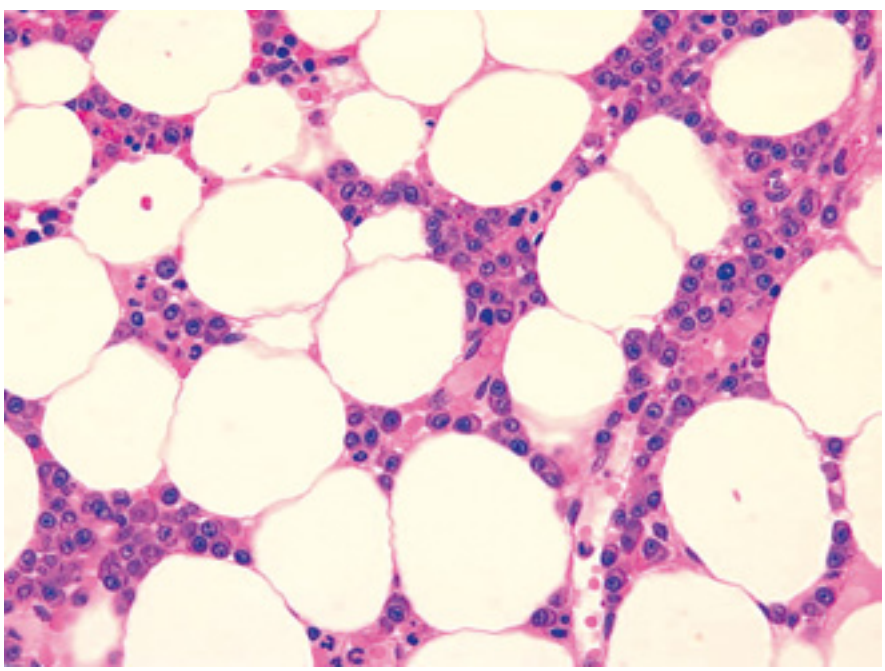

Fig. 7.2. Plasma cell myeloma. Interstitial infiltrate by plasma cells replaces the normal hematopoietic cells (H and E stain)

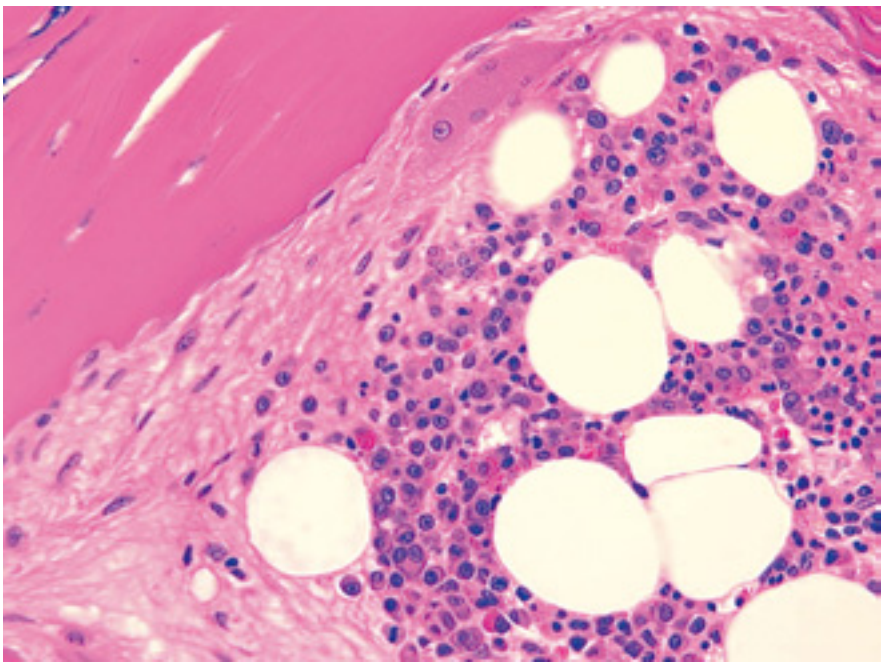

Fig. 7.3. Plasma cell myeloma. Large sheet of plasma cells near a bone trabeculae surrounded by collagenous fibrosis. Note an osteoclast, responsible for bone resorption, near the upper border (H and E stain)

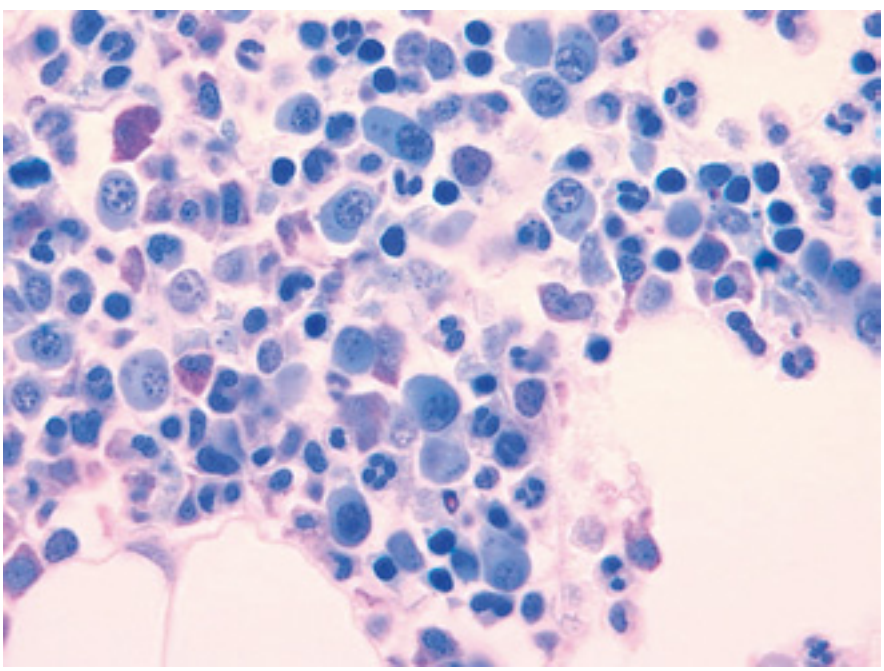

Fig. 7.4. Plasma cell myeloma. Interstitial infiltrate comprising mostly proplasma cells (Giemsa stain)

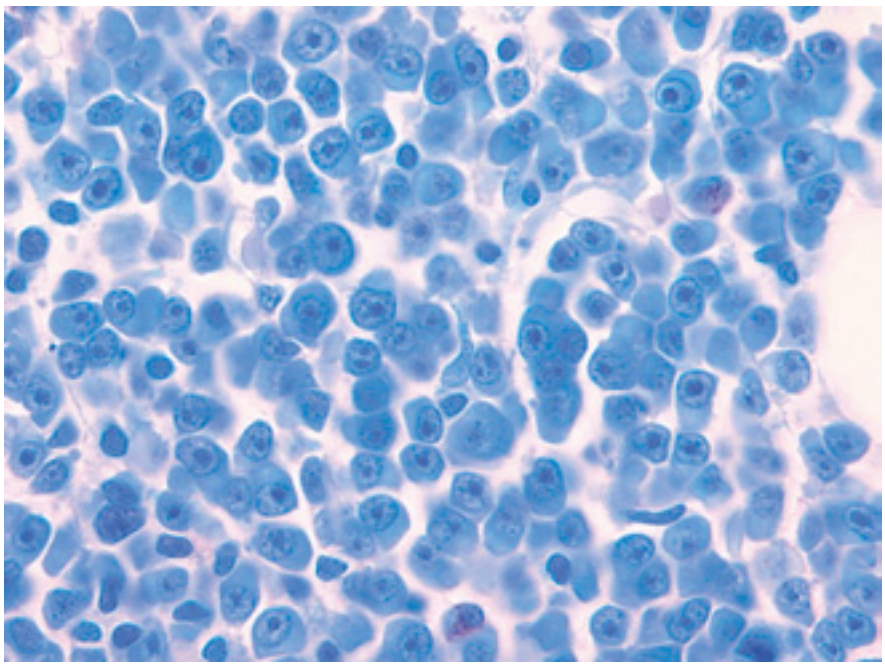

Fig. 7.5. Plasma cell myeloma. Massive involvement of large cells with the morphology of plasmablasts and immunoblasts (Giemsa stain)

plasm or in the nuclei. Proplasma cells are PAS-positive when they contain IgA. Immunoglobulin crystals may be seen in the cytoplasm of tumor cells, particularly in IgD myeloma (Gabriel et al. 1985). In some plasma cell myelomas, histiocytes accumulate around and between the tumor cells and may contain numerous immunoglobulin crystals (Gabriel et al. 1985).

A histological staging system of prognostic value that is based on the amount of tumor cells in the bone biopsy has been proposed (Bartl et al. 1982, 1987, 1995; Sailer et al. 1995):

- Stage I: less than 10 % of the bone marrow is involved
- Stage II: 20 – 50 % of the bone marrow is involved
- Stage III: More than 50 % of the bone marrow is involved

A classification system dividing plasma cell myeloma into four types (mature, intermediate, immature, and plasmablastic) based on the morphology of the tumor cells (Bartl et al. 1982, 1987, 1995; Sukpanichnant et al. 1994; Sailer et al. 1995) and having prognostic value has also been proposed.

Angiogenesis was recently demonstrated in bone marrow biopsies from multiple myeloma patients (Moehler et al. 2001b) and seems to be of prognostic significance. Angiogenesis and mast cell density increase simultaneously with progression of multiple myeloma (Ribatti et al. 1999). It appears that myelofibrosis develops simultaneously.

Cytology. Plasma cell myeloma can be diagnosed from smears obtained either by sternal puncture or by puncture of a bone tumor. While the diagnosis is based on the presence of more than 10 % plasma cells, the average plasma cell content is not enough. Severe plasmacytosis can be observed, for example, in infectious diseases (pneumonia, septicemia) as well as in dysimmune diseases, particularly Castleman's disease (Molina et al. 1996). Therefore, the increased number of plasma cells should be between 20 and 40 % (Kyle 1992; Reed et al. 1981; Brunning and McKenna 1994) and associated with an atypical morphology. The neoplastic cells mostly resemble mature plasma cells (Marschalko type), but they may be larger and some may exhibit various changes (Brunning and McKenna 1994; Diebold 1997): fraying of the cytoplasmic borders, cytoplasmic shedding, presence of hyaline inclusions, granules (Mott cells), vacuoles, crystalline inclusions of various size, multiple Russell bodies, and a deep-red cyto-

plasm (flame cells). The nucleus may also be larger, paler, with less condensed chromatin, more prominent nucleoli, and sometimes hyaline intranuclear inclusions. Some plasma cells may exhibit erythrophagocytosis or a Gaucher-like morphology. Beyond that, three peculiar patterns should be stressed:

1. The presence in about 10% of patients of larger cells with the morphology of plasmablasts, immunoblasts, or even unclassifiable multinucleated giant cells which can lead to a misdiagnosis of large-B-cell lymphoma.
2. The presence in about 2% of patients of pleomorphic cells that due to their notched, hyperlobulated nuclei resemble monocytes (Reed et al. 1981; Zukerberg et al. 1990).
3. The presence in about 5% of patients of cells resembling lymphocytes because of their dark nucleus and smaller size but with a basophilic ovoid cytoplasm; these cells have been called "lymphoplasmacytoid" or "lymphoid plasma cells" (Bartl et al. 1982, 1987, 1995). In these patients, there may be an erroneous diagnosis of B-cell chronic lymphocytic leukemia (B-CLL) with lymphoplasmacytoid differentiation or of lymphoplasmacytic lymphoma.

Immunohistochemistry is mandatory even on smears (see Chap. 4.2.1).

Immunohistochemistry

Plasma cell myeloma consists of mature B-cells expressing CD79α and the plasma-cell-associated antigens CD38 and CD138 (syndecan-1). The other B-cell-associated antigens, particularly CD20, are mostly negative. CD138 is an adhesion molecule and neoplastic plasma cells express other adhesion molecules such as CD56 and CD58, explaining perhaps the predominant settlement of the bone marrow (Ridley et al. 1993; Grogan et al. 2001). CD10 is sometimes also expressed (Van Riet et al. 1998) as well as cyclin D1.

Demonstration of intracytoplasmic immunoglobulin secretion with a light-chain restriction plays an important role in the diagnosis. Usually, the heavy-chain type is IgG, sometimes IgA, very rarely IgD, IgE, or IgM. About 85% of plasma cell myelomas produce a complete Ig with heavy- and light-chains. In 15% of these tumors, only one light-chain is produced by the neoplastic plasma cells (Bence Jones myeloma) (Grogan et al. 2001).

MUM1/IRF4 protein is the product of a homologous gene involved in the myeloma-associated t(6;14)(p25;q32). A new monoclonal antibody (MUM1p) demonstrates the presence of the protein in the nuclei of normal germinal center B-cells located predominantly in the "light zone" and with a morphology ranging from that of a centrocyte to that of a plasmablast/plasma cell (Falini et al. 2000). These cells do not express either Bcl-6 protein or Ki67 and are different from other germinal center cells that are MUM1-negative but positive for Bcl-6 and Ki67, and from mantle B-cells which are negative for all three proteins. PCR analysis of single MUM1+ cells isolated from germinal centers demonstrated rearranged Ig heavy-chain genes with a varying number of V_H somatic mutations, suggesting that these centrocytes may represent cells committed to exit the germinal center and to differentiate into plasma cells (Falini et al. 2000). MUM1 protein is strongly expressed in myeloma (Falini et al. 2000).

Immunohistochemistry using anti-CD34, anti-factor-VIII, or anti-CD31 is considered to be the gold standard in the detection of angiogenesis in bone marrow biopsies, but the permeability of the blood vessels cannot be determined (Mangi and Newland 2000; Moehler et al. 2001b). Vascular endothelial growth factor (VEGF) and interleukin-6 has also been used to demonstrate angiogenesis (Dankbar et al. 2000).

Genetic Features

Different types of genetic abnormalities have been disclosed (translocations, deletions, mutations) and are responsible for alteration of oncogenes and/or suppressor genes (Dewald et al. 1985). Chromosomes 1, 11, and 14 are most frequently involved. Translocation t(11;14) is common (Dewald et al. 1985). Three genes are present on chromosome 11 which play a role in disease evolution: (1) the neuronal-cell adhesion molecule (N-CAM) gene, located on 11q23; (2) the cyclin D1 gene, activated by the translocation near the IgH γ-switch region (Chesi et al. 1996); (3) the H-ras gene (p21), which has an effect on patient survival (Tsuchiya et al. 1988). Three other chromosomes may be involved: (1) the association of an abnormal chromosome 6 with increased secretion of tumor necrosis factor (TNF) which in turn is responsible for osteoclastic stimulation (Barlogie et al. 1989), (2) a deletion of the long arm of chromosome 7, associated with alteration of the multidrug resistance gene (drug resistance phenotype), (3) alteration of the PAX-5 gene on chromo-

some 9 resulting in the loss of CD19 expression (Mahmoud et al. 1996).

Chromosomal abnormalities have been disclosed in 18% of recently diagnosed patients and in 63% of patients with progressive disease (Barlogie et al. 1989). Fluorescent in situ hybridization (FISH) has recently been used to demonstrate the allelic loss of p53, predictive of an unfavorable evolution (Drach et al. 1998).

Immunoglobulin gene rearrangements are observed. In addition to monoclonal rearrangement, other rare types of rearrangement are compatible with oligoclonal or biclonal tumor development (Tsuchiya et al. 1988). Ig somatic mutations are frequently observed and are consistent with derivation of the tumor from a post-germinal-center B-cell. Patients with a light-chain restriction lose JH segments and/or parts of chromosome 14.

In some plasma cell myelomas, a γ-T-cell-receptor (TCR) gene rearrangement has been demonstrated.

Differential Diagnosis

In the majority of the cases, the diagnosis of plasma cell myeloma is easy, based on clinical presentation, cytology, histopathological pattern, and immunohistochemistry.

A severe *plasma cell hyperplasia*, representing 20–40% of the cells in the bone marrow, can be described in only a few non-neoplastic diseases. This reactive plasmacytosis has been described in patients with severe infections, for example, septicemia and pneumonitis, or in those with localized or multicentric Castleman's disease (Molina et al. 1996). Only mature polytypic plasma cells are present. The absence of atypical cells and the polytypic immunoglobulins represent the two criteria that allow this reactive plasmacytosis to be distinguished from plasma cell myeloma.

In early lesions of plasma cell myeloma, plasma cells may constitute less than 10% of the bone marrow hematopoietic cells. The diagnosis of plasma cell myeloma is based on the development of small nests of plasma cells at a distance from the capillaries and dispersed between adipose and the hematopoietic cells; on the existence of giant plasma cells, plasma cell precursors, and other atypical cells; and on the demonstration of monotypic cytoplasmic immunoglobulin in all these cells, contrasting with the polytypic pattern of the reactive plasma cells surrounding capillaries (Diebold 1997).

Another condition also raises difficult problems. *Massive osseous or juxtaosseous tumors consisting predominately of immunoblasts or plasmablasts* are very difficult to classify. There are almost no morphological or immunohistochemical criteria to distinguish between a large-B-cell lymphoma arising in a lymph node or in the soft tissue and extending into an adjacent bone or an extraosseous extension from a plasma cell myeloma transforming into an immunoblastic or plasmablastic variant. Only the clinical presentation may allow the distinction.

Occurrence

The sex ratio shows a male predominance of 3:2. The disease develops in adults over 35 years of age; the incidence increases with age.

Plasma cell myeloma accounts for 20–50% of primary bone tumors (Schajowicz 1994) and represents 1% of all malignant tumors (Kyle 1992). In the USA, the incidence is 2–3.9 cases per 100,000 people (Kyle 1992; Ries et al. 1991), representing 15% of all hematopoietic malignancies (Devesa et al. 1988). There is a higher incidence among black Americans (Schajowicz 1994), with myeloma being the most common lymphoid neoplasia in this population and the second most common in the white population (Devasa et al. 1988).

The incidence varies from one part of the world to the other, but in general increased to 45% from 1940 to the 1970s (Devesa et al. 1988). An increased risk of myeloma is observed after exposure to radiation, petroleum-derived pesticides, asbestos, rubber, plastic, and sawdust, and in response to chronic infection or persistent antigenic stimulation. Viral diseases may also play a role, for example, HIV and/or human herpes virus 8 (HHV8), which have been disclosed in bone marrow biopsy samples (Said et al. 1997). A "two-hit" hypothesis has been postulated in the pathogenesis of plasma cell myeloma, The disease probably develops from an end-stage B-cell, post-germinal-center, mature plasma cell (Hallek et al. 1998).

Clinical Presentation

Approximately 80% of the patients complain of localized or diffuse bone pain. In cases of vertebral localizations, sciatica or crural pain may be noted.

The first symptom in about 10% of the patients is a bone tumor in the ribs, sternum, or head.

Spontaneous fracture occurs as the presenting feature in about 5% of the patients.

Some patients also present with fever and weight loss.

Additional symptoms may be due to hyperviscosity syndrome, hypercalcemia, anemia, or amyloidosis.

Radiography of the skeleton discloses multiple round osteolytic lesions without sclerotic margins (Diebold 1997). These increase in size and coalesce, destroying the bone and the cortex which may appear very thin in the long bones, sternum, rib, and pelvis. Pathological fractures are observed in different bones, e.g. ribs or vertebrae with collapse of the vertebral bodies.

The bones involved are bone containing red marrow and with an active hematopoiesis, for example, vertebrae, ribs, skull, and pelvis in about 60 % of patients, and long bones, scapular, sternum, and mandible in about 40 % (Schajowicz 1994).

Immunoelectrophoresis shows a monoclonal gammopathy (IgG in 50 – 60 %, IgA in 20 – 35 %, rarely (2 %) IgD or IgE) in 99 % of the patients (Salmon and Cassady 1988), and a biclonal gammopathy with a light-chain restriction in 1 %. Monoclonal light-chain (Bence Jones protein) is disclosed in the serum of 15 % of patients and in the urine of 75 % (Salmon and Cassady 1988).

During disease evolution, renal insufficiency and recurrent bacterial infections are common.

Plasma cell myeloma is an incurable disease (Grogan et al. 2001). A great majority of the patients die after a median survival of 3 years. Only about 10 % survive at 10 years (Grogan et al. 2001). Increased tumor mass and poor renal function are associated with a shorter survival time.

A staging scheme was proposed by the WHO Classification 2001, based on tumor mass, renal function, hemoglobin level, serum calcium, assessment of lytic lesions, amount of M-component, and serum level of β2-microglobulin (poor survival in patients with a high level) (Rajkumar and Greipp 1999).

In addition, the percentage of infiltration of the bone marrow, classified in three stages, is of prognostic value (see Histopathology) (Bartl et al. 1982). Patients with immunoblastic or plasmablastic variants have a poor prognosis (Bartl et al. 1982; Greipp et al. 1998).

Recently, the increased amount of blood vessels due to angiogenesis in the bone marrow simultaneous with the growth of a neoplastic infiltrate has been studied by contrast-enhanced dynamic magnetic resonance imaging (Moehler et al. 2001a) and immunohistochemistry. Angiogenesis seems to be of prognostic value (Rajkumar et al. 2000; Moehler et al. 2001b).

7.1.1 Clinical Variants

Plasma cell myeloma presents with many variants.

7.1.1.1 Diffuse Decalcifying Myelomatosis

This variant is due to a diffuse infiltration of bone by plasma cells with severe bone rarefaction (osteoporosis).

It is characterized by the absence of lytic lesions on bone radiography; instead, there is diffuse decalcification (Kyle 1992; Bartl et al. 1982, 1987, 1995; Schajowicz 1994).

7.1.1.2 Osteosclerotic Myeloma

This variant is characterized by the development of large strands of collagen fibrosis that destroy the hematopoietic tissue of the bone marrow and by surrounding nests of plasma cells. Thickened bone trabeculae are surrounded by peritrabecular fibrosis with neoosteogenesis (Miralles et al. 1992). These lesions develop focally, either in one bone or in multiple sites. At a distance, plasma cell nests with atypical large cells may be present, but often only a few mature plasma cells are observed.

The plasma cells may produce either IgA or IgG, even sometimes IgM, with a high incidence (about 90 % of the tumors) of λ-light-chain restriction (Miralles et al. 1992).

In the differential diagnosis, all etiologies of osteomyelofibrosis have to be discussed: metastatic carcinoma, idiopathic myelofibrosis, myelofibrosis secondary to other chronic myeloproliferative disorders. The best criterion for diagnosing osteosclerotic myeloma is the discovery of monotypic (as determined by immunohistochemistry) plasma cell clusters in or between collagen bands.

Patients are often younger than those with typical plasma cell myeloma, and there is a male predominance. Anemia is rarely observed, in contrast to the occurrence of erythrocytosis and thrombocytosis. This type of myeloma is often associated with the so-called POEMS syndrome and/or with a pattern of lymphadenopathy typical of that in Castleman's disease (Miralles et al. 1992; Rolon et al. 1989).

7.1.1.3 Nonsecretory Myeloma

This variant of plasma cell myeloma can be defined as a myeloma without monoclonal immunoglobulin in the blood and urine (Bosman et al. 1996; Bourantas 1996).

The histopathological lesions are identical to those of typical plasma cell myeloma.

In the majority of these tumors, monotypic intracytoplasmic immunoglobulins can be demonstrated in the plasma cells. In very exceptional cases, it is impossible to disclose such immunoglobulin synthesis and the diagnosis can only be made based on morphology.

The patients present with the same clinical features as those with typical plasma cell myeloma but without any monoclonal component, due to the lack of excretion of the Ig synthesized by the plasma cells.

7.1.1.4 Solitary Myeloma (ICD-O: 9731/3*)

This type of plasma cell proliferation is responsible for a single bone tumor destroying either the central part of a short bone (vertebrae, rib) or of a long bone (Kyle 1992; Bataille and Sany 1981; Bacci et al. 1982; Bartl et al. 1982, 1987, 1995; Brunning and McKenna 1994; Guida et al. 1994; Schajowicz 1994).

Macroscopic study reveals that the cortex is thinned, but mostly without extension in the surrounding tissue. All of the histopathological patterns described for typical multiple myeloma can be observed; the immunohistochemistry is also identical to that of multiple myeloma.

Patients present with a single bone tumor, pain, and sometimes spontaneous fracture. In some patients, there is no monoclonal component in the blood or urine. Other patients may present with a low serum level of M-component.

Treatment of the tumor may be followed by complete remission with disappearance of the serum monoclonal component if present (Leibross et al. 1998). The risk of transformation into typical multiple plasma cell myeloma is high, occurring in about 55 % of the patients after 10 years of follow-up. Local recurrence is observed in about 10 % of the patients. Only 35 % seem to achieve complete remission (Kyle 1992).

* Given for solitary myeloma of the bone

7.1.1.5 Plasma Cell Leukemia

This type of leukemia can be detected before, or may be associated with bone manifestations (Kyle et al. 1974; Kyle 1992; Brunning and McKenna 1994; Dimopoulos et al. 1994; Garcia-Sanz et al. 1999).

Patients present with hepatosplenomegaly, thrombocytopenia, and a high level of LDH. The peripheral blood contains more than 20 % neoplastic plasma cells, which are hypodiploid with complex cytogenetic abnormalities (Garcia-Sanz et al. 1999).

The bone marrow is diffusely infiltrated. Liver biopsy reveals plasma cells in the lumen of hepatic sinuses.

Prompt chemotherapy is required. The median survival is about 20 months (Dimopoulos et al. 1994).

7.1.1.6 Variants with Peculiar Clinical Behavior

Plasma cell proliferations in fact comprise a broad spectrum of diseases, from the *monoclonal gammopathy of undetermined significance* (MGUS) (serum M-component less than the levels in myeloma, bone marrow plasmacytosis less than 10 % and no clinical signs or lytic bone lesions), which is often an incidental finding, to typical plasma cell myeloma with multiple lesions. Two clinical variants should be listed that fulfill some of the criteria for plasma cell myeloma but which are asymptomatic (Grogan et al. 2001). In *smoldering myeloma*, the serum M-component is at myeloma levels, there is a marrow plasmacytosis of 10 – 30 %, but no clinical or radiologic signs. In *indolent myeloma*, the serum M-component is at intermediate levels, marrow plasmacytosis is 10 – 30 %, there are up to three lytic bone lesions, but no other clinical or biological signs. Neither smoldering nor indolent myeloma requires immediate treatment..

7.2 Extraosseous (Extramedullary) Plasmacytoma (ICD-O: 9734/3)

Definition

Extraosseous (extramedullary) plasmacytoma is a neoplastic plasma cell proliferation developing outside the bone marrow, in the absence of a plasma cell myeloma.

Histology
These tumors are characterized by sheets of plasma cells infiltrating, destroying, and replacing normal tissue. The neoplastic cells show the morphology of mature plasma cells sometimes with giant plasma cells. In some cases, a variable number of proplasma cells, plasmablasts, or immunoblasts is recognized.

Immunohistochemistry and Genetic Features
Identical to those of plasma cell myeloma.

Differential Diagnosis
In all the localizations, plasmacytomas should be distinguished from chronic inflammatory diseases rich in plasma cells. The most important criterion is the demonstration of polytypic or monotypic immunoglobulin production.

In some sites (lymph node, spleen, tonsil, gastrointestinal tract, lung, skin, etc.), plasmacytomas should be distinguished from marginal zone lymphoma with a plasmacytic component and from lymphoplasmacytic lymphoma. The monoclonal immunoglobulin in these types of lymphomas is often IgM.

Clinical Features
Clinical presentation depends on the site. Extraosseous (extramedullary) plasmacytoma can arise in the upper respiratory tract (80% of the cases), gastrointestinal tract, lung, breast, thyroid, parotid gland, skin, testis, urinary bladder, central nervous system, as well as in lymphoid tissue (lymph node, spleen). There are no localizations in the bone marrow and no signs of plasma cell myeloma. A few patients only have a serum monoclonal component. Prognosis after radiotherapy in mostly good. There are local recurrences in about 25% of the patients, but transformation into a plasma cell multiple myeloma seems to be rare (Alexiou et al. 1999).

For more details, see the chapters on organ lymphomas.

7.3 Associated Diseases

7.3.1 Castleman's Disease

This peculiar disease of the lymph nodes may be either uni- or multicentric, the two subtypes of presentation probably corresponding to two different diseases.

Both subtypes have been observed in association with plasma cell myeloma, primary solitary bone plasmacytoma, and/or POEMS syndrome (Rolon et al. 1989). Some reported cases were associated with an HHV8 infection, particularly the multicentric variant occurring in HIV-positive patients.

7.3.2 POEMS Syndrome

The name of this syndrome is an acronym of the initials of the symptoms: *p*olyneuropathy, *o*rganomegaly (hepatomegaly, splenomegaly), *e*ndocrine disease (hypothyroidy, gynecomastia), *m*onoclonal immunoglobulin component in the blood, *s*kin lesions (thickening, hyperpigmentation, hypertrichosis).

The syndrome may be associated with Castleman's disease and/or with plasma cell myeloma often of the osteosclerotic variant (Miralles et al. 1992; Rolon et al. 1989).

This syndrome is probably due to the hyperproduction of cytokines (Klein 1995).

7.3.3 Primary Amyloidosis

Definition
Primary amyloidosis is characterized by the deposition in different tissues of a fibrillary protein (AL) with a β-pleated-sheet structure and consisting of immunoglobulin-light-chain (Kyle and Gertz 1990, 1995). Systemic AL amyloidosis involves the digestive tract, subcutaneous fat, and bone marrow, which are the sites that should be biopsied for the diagnosis. Numerous other organs or tissue can be involved: kidney, liver, spleen, heart, tongue, nerves.

Histology
The deposits are amorphous, eosinophilic (pink), acellular. They mostly predominate in the blood vessel walls, which are thickened, and on basement membranes. Perivascular and/or interstitial deposits can be observed and increase with progression. AL deposits stain with Kongo red showing green birefringence by polarization.

Differential Diagnosis
Systemic primary AL amyloidosis should be distinguished from other diseases caused by monoclonal immunoglobulin deposition; light-chain (mostly κ, i.e. Randall's syndrome), heavy-chain, or both light- and heavy-chains (de Lajarte-Thirouard et al. 1999).

These diseases are either associated with MGUS or with plasma cell myeloma. Deposits occur on basement membrane (glomerules, liver and spleen sinuses, bone marrow) or in joints. They are Congo-red-negative but can be characterized by immunohistochemistry (Preud'homme et al. 1994; Kambham et al. 1999).

Occurrence
AL amyloidosis occurs often in association with a plasma cell myeloma or an immunocytoma. About 20 % of patients with AL amyloidosis have a plasma cell myeloma and 15 % with plasma cell myeloma have primary AL amyloidosis.

Clinical Features
In some patients, systemic amyloidosis is disclosed fortuitously during the histological study of a biopsy, for example, a bone marrow biopsy.

Other patients present with symptoms that are unusual for a plasma cell myeloma: macroglossia, hepatosplenomegaly, congestive heart failure, malabsorption, peripheral neuropathy, bleeding, or nephrotic syndrome.

The suspected diagnosis should be confirmed by histolopathological evaluation of biopsies.

Myeloma patients with amyloidosis have a shorter survival (Kyle and Gertz 1990).

7.3.4 Light- and/or Heavy-Chain Deposition Diseases

Synonyms
- Randall disease

Definition
These diseases are characterized by a plasma cell proliferation associated with the deposition of a nonfibrillary amorphous material comprising immunoglobulin light-chains, heavy-chains, or both (Kambham et al. 1999).

These deposits are monoclonal, with a κ-light-chain predominance.

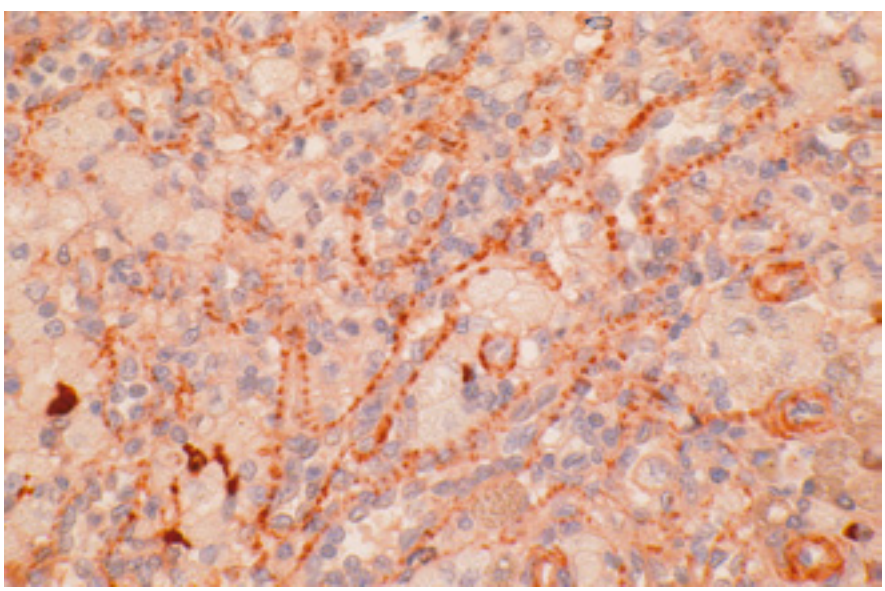

Fig. 7.6. Light-chain deposition disease. Deposition of immunoglobulin λ-light-chain on the basement membrane of the sinuses of the splenic red pulp

In contrast to the AL deposits of amyloidosis, these deposits do not have a β-pleated-sheet configuration.

Histology
These diseases are characterized by the deposition of an amorphous, eosinophilic, Congo-red-negative material on basement membranes of variable tissues: glomerules and tubules in the kidney (Preud'homme et al. 1994); sinusoids in the liver, spleen (Fig. 7.6) (De Lajarte et al. 1999), and bone marrow; nerves, heart, joints, and small vessels – the latter leading to vascular occlusion or microaneurysms.

Mostly, there are no plasma cells or only a few near the sites of deposition; however, the bone marrow is infiltrated by mature plasma cells, sometimes up to 60%.

Immunohistochemistry
The depositions are made of κ-light-chain in about 80% of the cases. In a few cases, heavy-chain is associated, mostly μ or γ. Sometimes only heavy-chain can be demonstrated. The cytoplasm of plasma cells in the bone marrow also has a light-chain restriction or a light-chain predominance (Kambham et al. 1999).

Genetic Features
The monoclonal immunoglobulin produced by the plasma cells shows structural changes due to deletions or mutations (Preud'homme et al. 1994). These changes are responsible for the deposition.

Differential Diagnosis
The most important disease to consider in the differential diagnosis is *primary amyloidosis*. In amyloidosis, the deposits are Congo-red- and thioflavin-positive, while these reactions are negative in monoclonal light-/heavy-chain deposition diseases.

Occurrence
This disease remains very rare. It occurs in adults between 30 and 80 years of age and without sex predominance (Grogan et al. 2001).

Clinical Presentation
The symptoms vary according to the main site of deposition: hepatomegaly, splenomegaly (De Lajarte-Thirouard et al. 1999), congestive heart failure, or often nephrotic syndrome and renal failure (Preud'homme et al. 1994). A monoclonal gammopathy is present in 85% of the patients, corresponding either to MGUS or sometimes to a typical myeloma (Kambham et al. 1999). Coagulopathy and hypocomplementemia have been observed.

The disease is rapidly fatal, survival being less than 2 years (Grogan et al. 2001) mostly due to variable visceral dysfunction, rarely to the plasma cell proliferation.

7.4 Heavy-Chain Diseases

Definition
These diseases are lymphoplasmacytic lymphomas in which only abnormal immunoglobulin heavy-chain is secreted.

μ-Heavy-Chain Disease. Bone marrow and lymph nodes show a diffuse infiltrate resembling that of B-CLL (Fig. 7.7). In association with small lymphocytes, it is possible to recognize plasma cells, often with a vacuolated cytoplasm. Macrophages containing PAS-positive material, sometimes crystallized, are dispersed between the lymphoid cells (Fig. 7.8)

The lymphoid cells express B-associated antigens (CD20, CD79α) and CD43 but are negative for CD5, CD10, and CD23. The plasma cells express CD38 and contain intracytoplasmic μ-heavy-chain, but light-chains cannot be demonstrated.

It is very difficult to distinguish μ-heavy-chain disease from B-CLL. The most important criterion is the discovery of typical vacuolated plasma cells.

Patients with this very rare lymphoma present with hepatosplenomegaly without adenopathy. The presence of μ-heavy-chain can be disclosed in the blood, but not in the urine, by immunoelectrophoresis. Light-chains (mostly κ) are found in the urine (Wahner-Roedler and Kyle 1992).

γ-Heavy-Chain Disease. Bone marrow and lymph node are diffusely infiltrated by an association of lymphocytes, lymphoplasmacytoid cells, mature plasma cells, a variable number of large cells with the morphology of immunoblasts, and some eosinophils. This pattern resembles lymphoplasmacytic lymphoma more than B-CLL.

Immunohistochemistry is identical to μ-heavy-chain disease with the exception of the γ-chain expression.

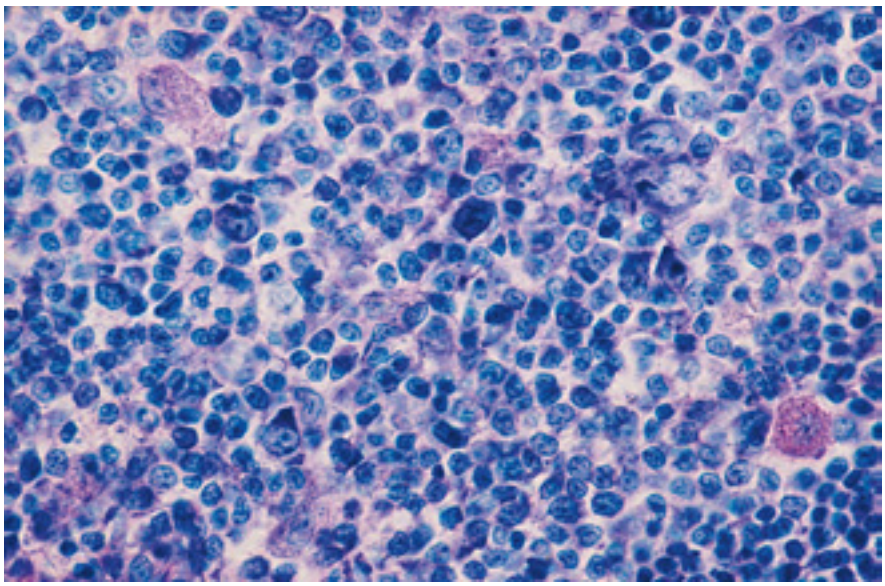

Fig. 7.7. μ-Heavy-chain disease. There is a diffuse infiltrate consisting of lymphocytes, lymphoplasmacytic cells, and plasma cells producing only μ-heavy chain without any light-chain. Rare dispersed immunoblasts and some histiocytes are seen (Giemsa stain)

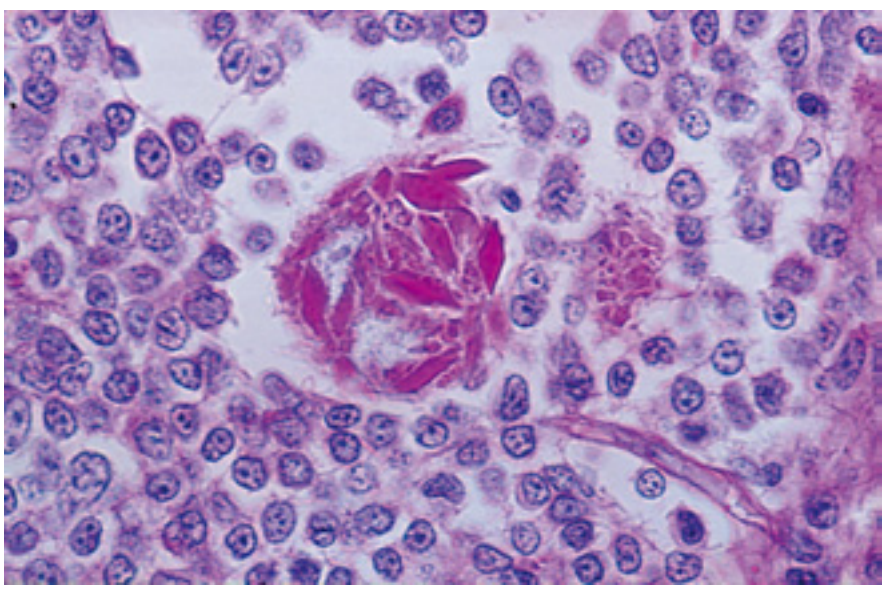

Fig. 7.8. Same patient as in Fig. 7.7. The histiocytes contain PAS-positive crystallized IgM (PAS stain)

It is difficult to distinguish γ-heavy-chain disease from lymphoplasmacytic lymphoma or, rarely, from B-CLL. Immunohistochemistry and peripheral blood immunoelectrophoresis are mandatory for the diagnosis.

This very rare disease occurs in adults with a median age of 60 years. Patients complain of anorexia, weight loss, and fever and present with peripheral adenopathies and hepatosplenomegaly. Involvement of Waldeyer's ring is very characteristic. Often, infections occur. Peripheral blood lymphocytosis mimics that of B-CLL. Immunofixation discloses the presence of γ-heavy-chain in the blood. Disease evolution is variable from patient to patient; in some there is an indolent course, while in others progression is very rapid and aggressive (Franklin et al. 1979; Fernand and Brouet 1999).

α-*Heavy-Chain Disease.* The lamina propria of the small intestine is diffusely and massively infiltrated by mature plasma cells associated with small lymphocytes. This infiltrate is responsible for the atrophy of the glands and villi (Galian et al. 1972). Lymph nodes may be infiltrated in untreated patients. Transformation into a more aggressive lymphoma consisting of plasmablasts, immunoblasts, or even giant cells with a Reed-Sternberg-like morphology has been observed. This type of transformation is responsible for the development of localized tumor along the intestine and of voluminous mesenteric adenopathies (Galian et al. 1972). A very few cases have been described in which the disease involves the respiratory tract.

The immunohistochemistry is identical to that of other heavy-chain diseases except for the presence of α-chain.

This disease represents a variant of MALT lymphoma, a mucosae-associated marginal zone lymphoma. The most difficult aspect of the differential diagnosis is to rule out an exceptional plasmacytoma of the intestine in which there is a solid localized tumor rather than the characteristic diffuse infiltrate of the mucosae.

This type of heavy-chain disease occurs mostly in children, adolescents, and young adults, particularly those living in the Mediterranean area under poor socioeconomic conditions.

It is interesting to note that in countries such as Lebanon, Egypt, Saudi Arabia, and North Africa this disease has more or less disappeared (personal experience).

Patients complain of abdominal pain, fever, diarrhea with steatorrhea, and malabsorption. α-Heavy-chain is present in gut secretions and in the peripheral blood.

Antibiotics given at the beginning of the disease results in a complete clinical and histological remission.

In patients treated later on in the course of the disease, remission is incomplete or absent. Furthermore, there is a risk of transformation of the disease into an aggressive lymphoma of immunoblastic type with plasmacytoid differentiation or of plasmablastic type, both of which have a rapid fatal evolution (Seligman 1975; Fernand and Brouet 1999).

References

Alexiou C, Kau RJ, Dietzfelbinger H et al (1999) Extramedullary plasmacytoma: tumor occurrence and therapeutic concepts. Cancer 85:2305–2314

Bacci G, Calderoni P, Cervellati C, Zambaldi A (1982) Solitary plasmacytoma of bone: a report of 19 cases. Ital J Orthop Traumatol 8:469–478

Barlogie B, Epstein J, Selvanayagam P, Alexanian R (1989) Plasma cell myeloma – new biological insights and advances in therapy. Blood 73:865–879.25

Bartl R, Frisch B, Burkhardt R et al (1982) Bone marrow histology in myeloma: its importance in diagnosis, prognosis, classification and staging. Br J Haematol 51:361–375

Bartl R, Frisch B, Fateh-Moghadam A, Kettner G, Jaeger K, Sommerfeld W (1987) Histologic classification and staging of multiple myeloma. A retrospective and prospective study of 674 cases. Am J Clin Pathol 87:342–355

Bartl R, Frisch B, Wilmanns N (1995) Morphology of multiple myeloma. In: Malpas JS, Bergsagel DE, Kyle RA (eds) Myeloma: biology and management. Oxford University Press, Oxford, pp 82–123

Bataille R, Sany J (1981) Solitary myeloma: clinical and progostic features of a review of 114 cases. Cancer 48:845–851

Bosman C, Fusilli S, Bisceglia M, Musto P, Corsi A (1996) Oncocytic nonsecretory multiple myeloma. Acta Haematol 96:50–56

Bourantas K (1996) Nonsecretory multiple myeloma. Eur J Haematol 56:109–111

Brunning RD, McKenna RW (1994) Tumors of the bone marrow. Atlas of tumor pathology. AFIP, Washington DC, pp 323–350

Chesi M, Bergsagel L, Brents L, Smith C, Gerhard D, Kuehl W (1996) Dysregulation of cyclin D1 by translocation into an IgH gamma switch region in two multiple myeloma cell lines. Blood 88:647–681

Dankbar B, Padro T, Leo R, Feldmann B, Kropff M, Mesters RM, Serve H, Berdel WE, Kienast J (2000) Vascular endothelial growth factor and interleukin-6 in paracrine tumor-stromal cell interactions in multiple myeloma. Blood 95:2630–2636

De Lajarte-Thirouard AS, Molina T, Audouin J, Le Tourneau A, Leduc F, Rose C, Diebold J (1999) Spleen localization of light-chain deposition disease associated with sea-blue histiocytosis revealed by spontaneous rupture. Virchows Arch 434:463–465

Devesa SS, Silverman DT, Young JL Jr et al (1988) Cancer incidence and mortality trends among whites in the United States 1947–84. J Natl Cancer Inst 79:701–770

Dewald GW, Kyle RA, Hicks GA, Greipp PR (1985) The clinical significance of cytogenetic studies in 100 patients with multiple myeloma, plasma cell leukemia, or amyloidosis. Blood 66:380–390

Diebold J (1997) Myeloma. In: Forrest M, Tomeno B, Vanel D (eds) Orthopedic surgical pathology. Churchill Livingstone, Edinburgh, pp 491–500

Dimopoulos MA, Palumbo A, Delasalle KB, Alexanian R (1994) Primary plasma cell leukemia. Br J Haematol 88:754–759

Drach J, Ackermann J, Fritz E et al (1998) Presence of a p53 gene deletion in patients with multiple myeloma predicts for short survival after conventional-dose chemotherapy. Blood 92:802–809

Falini B, Fizzotti M, Pucciarini A, Bigerna B, Marafioti T, Gambacorta M, Pacini R, Alunni C, Natali-Tanci L, Ugolini B, Sebastiani C, Cattoretti G, Pileri S, Dalla-Favera R, Stein H (2000) A monoclonal antibody (MUM1p) detects expression of the MUM1/IRF4 protein in a subset of germinal center B-cells, plasma cells and activated T cells. Blood 95:2084–2092

Fernand JP, Brouet JC (1999) Heavy-chain diseases. Hematol Oncol Clin North Am 13:1281–1294

Franklin EC, Kyle R, Seligmann M, Frangiona B (1979) Correlation of protein structure and immunoglobulin gene organization in the light of two new deleted heavy chain disease proteins. Mod Immunol 16:919–921

Galian A, Lecestre MJ, Scotto J, Bognel C, Matuchansky C, Rambaud JC (1972) Pathological study of alpha chain disease with special emphasis on evolution. Cancer 39:2081–2101

Garcia-Sanz R, Orfao A, Gonzalez M et al (1999) Primary plasma cell leukemia: clinical, immunophenotypic, DNA ploidy, and cytogenetic characteristics. Blood 93:1032–1037

Gabriel L, Escribano L, Perales J, Bellas C, Odriozola J, Navarro JL (1985) Multiple myeloma with crystalline inclusions in most hematopoietic cells. Am J Hematol 18:405–411

Greipp PR, Leong T, Bennett JM et al (1998) Plasmablastic morphology and independent prognostic factor with clinical and laboratory correlates: Eastern Cooperative Oncology Group (ECOG) myeloma trial E9486 report by the ECOG Myeloma Laboratory Group. Blood 91:2501–2507

Grogan TM, Van Camp B, Kyle RA, Müller-Hermelink HK, Harris NL (2001) Plasma cell neoplasms. In: Jaffe JS, Harris NL, Stein H, Vardiman JW, (eds) World Health Organization Classification of Tumors. Pathology and genetics of tumors of hematopoietic and lymphoid tissues. IARC Press, Lyon

Guida M, Casamassima A, Abbate I et al (1994) Solitary plasmacytoma of bone and extramedullary plasmacytoma: 2 different nosological entities? Tumori 80:370–377

Hallek M, Bergsagel PL, Anderson KC (1998) Multiple myeloma: increasing evidence for a multistep transformation process. Blood 91:3–21

Kambham N, Markowitz G, Appel G et al (1999) Heavy chain deposition disease: the disease spectrum. Am J Kidney Dis 33:954–962

Klein B (1995) Cytokine, cytokine receptors, transduction signals, and oncogenes in human multiple myeloma. Semin Hematol 32:4–19

Kyle RA (1992) Diagnostic criteria of multiple myeloma. Hematol Oncol Clin North Am 6:347–358

Kyle RA, Gertz MA (1990) Systemic amyloidosis. Crit Rev Oncol Hematol 10:49–87

Kyle RA, Gertz MA (1995) Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol 32:45–59

Kyle RA, Maldonado JE, Bayrd ED (1974) Plasma cell leukemia. Report of 17 cases. Arch Intern Med 133:813–818

Leibross RH, Ha CS, Cox JD, Weber D, Delasalle K, Alexanian R (1998) Solitary bone plasmacytoma: outcome and prognostic factors following radiotherapy. Int J Radiat Oncol Biol Phys 41:1063–1067

Mahmoud M, Huang N, Nobuyoshi M, Lisuov I, Tanake H, Kawano M (1996) Altered expression of PAX-5 gene in human myeloma cells. Blood 87:4311–4315

Malpas JS, Bergsagel DE, Kyle RA (eds) (1995) Myeloma: biology and management. Oxford University Press, Oxford

Mangi MH, Newland A (2000) Angiogenesis and angiogenic mediators in haematological malignancies. Br J Haematol 111:43–51

Miralles GD, O'Fallon KR, Talley NJ (1992) Plasma-cell dyscrasia with polyneuropathy. The spectrum of POEMS syndrome. N Engl J Med 327:1919–1923

Moehler TM, Hawighorst H, Neben K, Egerer G, Max R, van Kaick G, Ho AD, Goldschmidt H (2001a) Bone marrow microcirculation analysis in multiple myeloma by contrast-enhanced dynamic magnetic resonance imaging. Int J Cancer 93:862–868

Moehler TM, Neben K, Ho AD, Goldschmidt H (2001b) Angiogenesis in hematologic malignancies. Ann Hematol 80:695–705

Molina T, Brouland JP, Bigorgne C, Le Tourneau A, Delmer A, Audouin J, Diebold J (1996) Plasmocytose médullaire pseudo-myélomateuse au cours d'une maladie de Castleman multicentrique. A propos d'une observation. Ann Pathol 16:133–136

Preud'homme J, Aucouturrier P, Touchard G et al (1994) Monoclonal immunoglobulin deposition disease (Randall type). Relationship with structural abnormalities of immunoglobulin chains. Kidney Int 46:965–972

Rajkumar SV, Greipp PR (1999) Prognostic factors in multiple myeloma. Hematol Oncol Clin North Am 13:1295–1314

Rajkumar SV, Leong T, Roche PC, Fonseca R, Dispenzieri A, Lacy MQ, Lust JA, Witzig TE, Kyle RA, Gertz MA, Greipp PR (2000) Prognostic value of bone marrow angiogenesis in multiple myeloma. Clin Cancer Res 6:3111–3116

Reed M, McKenna RW, Bridges R, Parkins J, Frizzera G, Brunning RD (1981) Morphologic manifestations of monoclonal gammopathies. Am J Clin Pathol 76:8–23

Ribatti D, Vacca A, Nico B, Quondamatteo F, Ria R, Minischetti M, Marzullo A, Herken R, Roncali L, Dammacco F (1999) Bone marrow angiogenesis and mast cell density increase simultaneously with progression of human multiple myeloma. Br J Cancer 79:451–455

Ridley R, Xiao H, Hata H et al (1993) Expression of syndecan regulates human myeloma plasma cell adhesion to type 1 collagen. Blood 81:767–774

Ries LA, Hankey BF, Miller BA, Hartman AM, Edwards BK (1991) Cancer statistics review 1973–1988. National Cancer Institute NIH Publ 91:2789

Rolon PG, Audouin J, Diebold J, Rolon PA, Gonzalez A (1989) Multicentric angiofollicular lymph node hyperplasia associated with a solitary osteolytic costal IgG lambda myeloma. POEMS syndrome in a South American (Paraguayan) patient. Pathol Res Pract 185:468–475

Said J, Rettig M, Heppner K et al (1997) Localization of Kaposi's-associated herpes virus in bone marrow biopsy samples from patients with multiple myeloma. Blood 90:4278–4282

Sailer M, Vykoupil KF, Peest D, Cordewey R, Deicher H, Georgii A (1995) Prognostic relevance of a histologic classification system applied in bone marrow biopsies from patients with multiple myeloma. A histopathological evaluation of

biopsies from 153 untreated patients. Eur J Haematol 54:137–146
Salmon SE, Cassady JR (1988) Plasma cell neoplasms, chap 54. In: DeVita VT, Hellman S, Rosenberg S (eds) Cancer, principles and practice of oncology. Lippincott, Philadelphia
Schajowicz F (1994) Tumors and tumorlike lesions of bone, 2nd edn. Springer, Berlin Heidelberg New York
Seligmann M (1975) Immunochemical, clinical, and pathological features of alpha-heavy chain disease. Arch Intern Med 135:78–82
Sukpanichnant S, Cousar JB, Leesasiri A, Graber SE, Greer JP, Collins RD (1994) Diagnostic criteria and histologic grading in multiple myeloma: histologic and immunohistologic analysis of 176 cases with clinical correlation. Hum Pathol 25:308–318
Tsuchiya H, Epstein J, Selvanayagam P et al (1988) Correlated flow cytometric analysis of H-ras p21 and nuclear DNA in multiple myeloma. Blood 72:796–800
Van Riet I, Vanderkerken K, De Greef C, Van Camp B (1998) Homing behaviour of the malignant cell clone in multiple myeloma. Med Oncol 15:1554–1564
Wahner-Roedler DL, Kyle RA (1992) Mu-heavy chain disease: presentation as a benign monoclonal gammopathy. Am J Hematol 40:56–60
Zukerberg IR, Ferry JA, Conlon M, Harris NL (1990) Plasma cell myeloma with cleaved multilobated and monocytoid nuclei. Am J Clin Pathol 93:657–661