MINISTRY OF HEALTH OF THE REPUBLIC OF MOLDOVA

„NICOLAE TESTEMITANU" STATE UNIVERSITY OF MEDICINE AND PHARMACY

Musteata Vasile

INSIGHTS INTO BIOLOGY, DIAGNOSIS AND TREATMENT OF MULTIPLE MYELOMA

(methodical guidelines for students)

CHIȘINAU, 2021

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CONTENTS

LIST OF ABBREVIATIONS

MM – multiple myeloma,
MGUS – monoclonal gammopathy of undetermined significance,
CDKN2A – cyclin-dependent kinase inhibitor A,
CDKN2C– cyclin-dependent kinase inhibitor C,
CD – cluster of differentiation,
BM – bone marrow,
FISH – fluorescence in situ hybridization,
TGF-β – transforming growth factor β,
IgH – immunoglobulin heavy chain,
MRI – magnetic resonance imaging,
CT – computed tomography,
ECOG – The Eastern Cooperative Oncology Group,
WHO – Word Health Organisation,
MDE – myeloma defining events,
HSCT – hematopoietic stem cell transplantation,
OS – overall survival,
PFS – progression-free survival

INSIGHTS INTO BIOLOGY, DIAGNOSIS AND TREATMENT OF MULTIPLE MYELOMA

Definition

Multiple myeloma (MM) is a B-cell malignancy, characterized by clonal proliferation of malignant plasma cells in the bone marrow, production of monoclonal protein secreted into the blood and urine, as well as being associated with the organ and skeletal system involvement [1,2,3,4]. The first documented case of MM was reported by Dr. Samuel Solly in 1844, following an autopsy on a patient who died within 4 years after anemia and bone fractures. MM was previously known as Kahler's disease due to the description of a case with that pathology by the professor Otto Kahler from Prague [5]. Over the last two decades, a significant progress has been made in the diagnosis and treatment of MM, especially related to the implementation of immunophenotyping, cytogenetic examinations, autologous stem cell transplantation and proteasome inhibitors. However the disease remains incurable in most cases, thus significantly affecting both patients' quality of life and life expectancy.

Preface

These methodical guidelines comprise the basic topics necessary for medical students to make the diagnosis of MM, as well as elaborate treatment principles and personalized treatment strategies. The methodical guidelines constitute an effort to make the subject issues on MM available, thus being perceived by the students. The major objective is to support the students of the Faculties of Medicine and Public Health. There have been defined the notions that will allow enriching the knowledge related to this field, as well as will provide useful data at all steps of knowledge assessment. An appropriate attention will be paid to the clinical activity of the students at the patient's bed, when carrying out practical skills, tests and clinical cases on the given subject. In order

to achieve a better understanding of the subject issues presented in these methodical guidelines, we opted for using graphical materials (tables, figures, and diagrams), images, clinical cases and control tests.

Duration of the seminar

The seminar lasts 5 hours.

The aim of the seminar

To study the epidemiological patterns, etiology, pathogenesis, clinical features, laboratory tests and health care options applied for diagnosing MM, synthesis of treatment principles and personalized strategies.

Objectives of the seminar

1. To build-up knowledge on the epidemiology, etiology and pathogenesis of MM;
2. To develop knowledge on the clinical, hematological, morphological, immunophenotyping and cytogenetic features of MM;
3. To acquire practical skills in MM diagnosis;
4. To build-up knowledge on differential diagnosis of MM;
5. To develop general principles and personalized strategies of MM treatment.

The seminar will be proceeded

1. On Hematology Discipline, at "NicolaeTestemitanu" SUMPh, in groups of students, by using study modules.
2. Within the Hematology units at the Hematology Department of the PMSI Institute of Oncology of the Republic of Moldova.
3. Within the Hematology centers at the Consulting Diagnostic Centre of the PMSI Institute of Oncology of the Republic of Moldova.

Methods and Materials used for the seminar

Teaching methods to be used

Teaching methods and procedure, involved in the effective learning and achievement of the suggested objectives, are as following:

- presentation of the subject by formulation of definitions, description, explanation and demonstration;
- joint interactive discussion;
- problem-solving cases;
- data summarizing and synthesizing.

Various forms of independent, frontal, group, interactive activities are used at the seminars.

Methods of evaluation

- questioning on the study issue;
- problem-solving situations;
- analysis of clinical cases;
- single choice and multiple choice tests;
- individual work;
- assessment of practical skills;
- taking exam.

Materials for the seminar

Teaching materials such as tables, schemes, algorithms, digital images, international guidelines are used for broader learning of CLL. Power Point presentations are also applied during the seminars.

Questions for students' self-training

1. Epidemiology and etiology of MM.
2. Pathogenesis of MM.
3. Clinical features, types and complications of MM.
4. MM diagnosis.
5. MM staging.
6. The value of immunophenotyping and immunohistochemistry in diagnosing MM

7. The value of cytogenetic and molecular examinations in diagnosing MM
8. The value of radiological imaging in diagnosing MM.
9. Differential diagnosis of MM.
10. Principles of management and treatment options in MM.
11. Evolution and prognosis of MM.

Epidemiology of MM

According to the specialized literature data and references, the MM-related morbidity rate varies between 1.4 - 7 cases per 100,000 population [6,7]. The incidence rate increases steadily with age, with a peak age-specific morbidity rate of nearly 40-50 cases per 100,000 in men and 25-30 cases per 100,000 in men over 75 years old[8,9]. The disease makes up 1% of all cases of malignant neoplasms and 10-15% of cases of malignant haematological diseases. In 2019, MM accounted for approximately 0.8% 14,000) of all new cancer cases annually and 0.9% (63,000) of all cancer deaths worldwide [10]. Approximately 6500 new cases are diagnosed with MM annually in Germany and 30330 of new cases are registered in the USA. Among different countries the median age at the onset of MM varies between 66-71 years. The onset of the disease in the age groups under 45 is less common, accounting for 2% of cases.

Etiology of multiple myeloma

The etiology of the disease has not been sufficiently studied yet. Ionizing radiation, pesticides, benzene derivatives, obesity and chronic infections are reported as favouring factors of MM development [2,7]. However, there is a small number of documented cases, thus more data are required to establish a significant relationship. MM and MGUS have been reported in familial clusters. Arelationship between MM and pre-existing inflammatory diseases has been suggested, whereas plasma cell disorders associated with protracted stimulation of the reticuloendothelial system have also been reported in experimental studies. Nevertheless, more recent case-control studies do not support the impact of

chronic antigenic stimulation in the etiopathogenesis of MM. In ethnic terms, people of color have a double risk of developing MM.

Pathogenesis of multiple myeloma

In most patients, MM is installed on the underlying monoclonal gammopathy of uncertain significance (MGUS), with a staged evolution into incandescent myeloma (asymptomatic) and symptommatic myeloma. The disease develops from the premalignant proliferation of monoclonal plasma cells, being derived from post-germinal central B cells [6,7]. Chromosomal aberrations are detected by FISH cytogenetic examination in over 90% of MM cases and are the key elements of pathogenesis. Some of these represent early chromosomal translocations and deletions in the immunoglobulin switching region on chromosome 14 (q32.33). Genetic dysregulation occurs, especially of the MMSET gene in all cases and FGFR3 in 30% of cases. Late genetic translocations and mutations involved in disease progression include karyotypic aberrations in MYC, activation of KRAS and NRAS protein encoding oncogenes, mutations in FGFR3 and TP53, and inactivation of CDKN2A and CDKN2C family genes *(Figure 1)* [6,11].

The interactions of myeloma cells, stromal bone marrow cells and extracellular matrix proteins, mediated by cell surface receptors (integrins, cadherins and selectins), increase the tumor growth, survival and migration, as well as the drug resistance. In 10 - 20% of cases with MM, the mutation of the p53 tumor growth suppressor gene is found, which contributes to tumor progression. That mutation is associated with generalized forms and aggressive clinical evolution of MM. The interleukin 6 is a major stimulator of myeloma cell proliferation and differentiation. The aggressive evolution and progression of MM are determined by the high serum level of interleukin 6 and the increased number of interleukin 6 receptors on the surface of plasma cells. The effect of interleukin 6 is intensified by interleukin 1 and GM-CSF. Interleukins 3 and 5 stimulate the production of interleukin 6 receptors by myeloma cells. Myeloma cells secrete interleukin 1β, which partici-

pates in the processes of molecular adhesion, activates osteoclasts and the production of interleukin 6, contributes to the dissemination of myeloma cells, being one of the components of osteoclast-activating factor. The osteoclast-activating factor triggers the function of osteoclastic cells, thus causing osteolysis with the removal of calcium ions from the bones. The current pathogenic models assume that MM develops through a multistep transformation from normal plasma cells to MGUS, which suggests plasma cells immortalization and, subsequently, the transformation to active MM, where clonal plasma cells cause end-organ damage [2]. Cytogenetic studies using FISH have demonstrated that most genetic lesions typical of MM may already occur at MGUS stage.

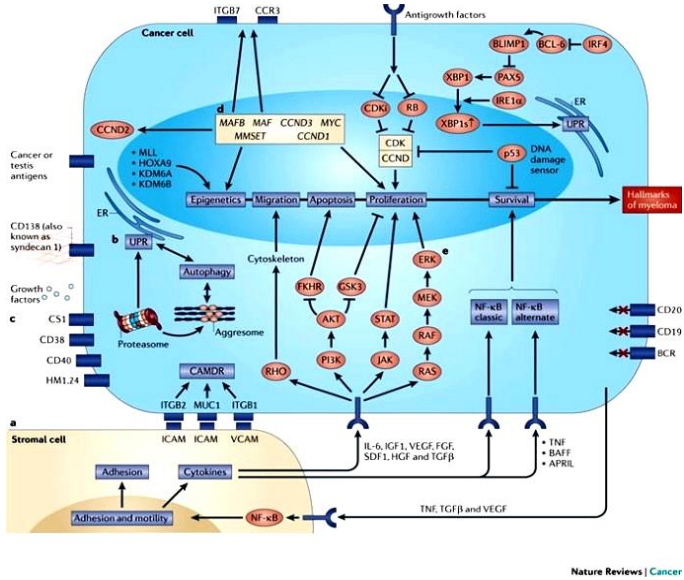

Figure 1. **Pathogenesis of MM** [Morgan G.J., Walker B.A., Davies F.E.*Nature Reviews Cancer*. 2012; vol. 12]

Clinical features, types and complications of multiple myeloma

MM is characterized by two main syndromes - osteomedullary and protein pathology. Osteomedullary syndrome is due to the bone marrow involvement with the development of anemia, osteodestruction with pathological fractures and hypercalcaemia [2,12]. Bone pain is one of the initial clinical symptoms of MM in 70% of cases. The bones of the axial skeleton are commonly affected, especially the vertebrae, clinically manifestingas radiculopathy. Spinal cord may be affected in cases of compressed vertebral fractures and intervertebral extension of the tumor process, with the development of paraparesis or lower paraplegia. The proximal segments of the tubular bones (humerus and femur) are more frequently involved. Bone pain, swelling in the areas of the bone involvement and fractures form the Kahler triad. Anemia of varying degrees is manifested by asthenia, vertigo, headache, dyspnea and heart palpitations. Hypercalcemia at the time of diagnosis is detected in 20-40% of cases with MM. Hypercalciemiamay cause nausea, vomiting, drowsiness, temporal and spatial disorientationandcoma, thus resulting in chronic renal failure. Visceral involvement, especially hepatosplenomegaly, is found in 5 to 13% of patients. Hyperproteinemialeads tohyperviscosity with the onset of retinopathy, myeloma nephropathy with chronic renal failure, cerebral and peripheral microcirculation disorders with Raynaud's syndrome-like pain. Hyperproteinemia and hypercalcaemia contribute to renal tube obstruction, stasis, necrosis of epithetlium, development of connective tissue and nephrosclerosis. According to the literature references, chronic renal failure may be the cause of death in approximately 30-35% of MM patients. Hyperproteinemia and hyperviscosity are marked in the immunological types A and M.

Clinical types of MM: symptomatic MM, extramedullary disease in MM (soft tissue and/or visceral involvement), smoldering or indolent myeloma (plasma monoclonal immunoglobulin $\leq$ 4.5 g/dL; there is no evidence of end-organ disorder related to the clonal plasma cell disorder, no lytic bone lesions on complete skeletal X-ray exam or other imaging

tests, no clinical and laboratory features of paraamyloidosis or light chain depositions), solitary plasmacytoma of bone.

MM is characterized by an immunodeficiency status and frequent infectious complications due to deficiency of antibodies as a result of the substitution of normal plasma cells by tumor cells. Infections are the leading cause of morbidity and mortalityin myeloma patients [13]. Infections are not only related to dysfunction of the immune system intrinsic to myeloma, however these are caused by other factors, including the therapeutictype and duration (cytotoxic agents, glucocorticoids, autologous/allogeneic hematopoietic stem cell transplantation), age, and coexisting comorbidities. Extensive immunologic abnormalities involving both the innate and adaptive immune system have been reported in myeloma. Hypogammaglobulinemia reflecting suppression of CD19+ B lymphocytes results in susceptibility to encapsulated organisms, such as Streptococcus pneumoniae and Haemophilus influenzae. Deficiencies in cellular immune function account for the recurrent infections commonly seen in myeloma. Dendritic cells are highly specialized antigen-presenting cells central to the induction of cellular and humoral immune response. Dendritic cells have a reduced capacity to stimulate antigen specific T cells and present patient-specific idiotype to autologous T cells. A number of cytokines present in the myeloma microenvironment may be responsible for these abnormallities, including TGF-β, IL-6, and IL-10. Abnormalities in T-cell function include reversed CD4+/CD8+ T-cell ratios, severe disruptions in the T-cell repertoire, and abnormal intracellular signal transduction impairing T-cell activation.

Due to the demyelination of nerve fibers under the action of paraproteins, sensory neuropathy is installed in 5% of cases. Neurologic disorders are also caused by regional myeloma cell growth compressing the spinal cord or cranial nerves [2,13]. Polyneuropathies are observed with perineuronal or perivascular amyloid deposition and can also be seen with osteosclerotic myeloma, sometimes as part of the complete polyneuropathy, organomegaly, endocrinopathy, monoclonal gammo-

pathy, and skin changes (POEMS) syndrome. The vascular endothelial growth factor appears to be the central cytokine.

Paraproteinemia contributes to the development of paraamyloidosis in 15% of patients with MM, with damage to collagen-opulent organs: muscles (heart, tongue), skin, tendons, joints, vascular adventitia. Thus, paraamyloidosis may be manifested clinically by heart failure, dermatosis, arthrosis with arthralgia, gastrointestinal disorders.

Hyperviscosity occurs in less than 10% of patients with MM [2,13]. Symptoms of hyperviscosity result from circulatory problems, leading to cerebral, pulmonary, renal, and other organ dysfunction. Hyperviscosity is often associated with bleeding. While there is a general correlation between clinical symptoms and relative serum viscosity, the relationship between serum immunoglobulin levels and symptoms are not the same from one patient to the other. This may be related to the different physicochemical properties of each of the classes and subclasses of immunoglobulin molecules. Because of a greater tendency for IgA to form polymers, patients with IgA myeloma have hyperviscosity more commonly (nearly one- third) than patients with IgG myeloma.

The renal involvement occurs in 30-50% of myeloma patients at time of diagnosis, with up to 10% of patients requiring hemodialysis during their course of management [13]. Myeloma cast nephropathy is the most common cause of renal impairment and is also referred to as myeloma kidney. Disorders of renal function occur when the tubular absorptive capacity for light chains is exhausted, resulting in the formation of tubular casts in the distal nephron formed by the binding of light chains to uromodulin. These tubular casts obstruct the distal nephron and parts of the ascending loop of Henle and contribute to development of interstitial nephritis. There is a considerable variation in the nephrotoxic proclivity of light chains and some patients may have minimal light-chain secretion and present with renal impairment before other manifestations of myeloma appear. The second most common cause of nephropathy is hypercalcemia. Concomitant hypercalciuria leads to volume depletion and prerenal azotemia. In addition, hypercalcemia leads to cal-

cium storage in the renal tubules, which also result in interstitial nephritis. Paramyloidosis associated with light-chain immunoglobulin proteinuria usually presents as the nephrotic syndrome, with very little light-chain secretion in the urine, but can lead, over time, to renal failure. Amyloid deposits can be found everywhere within the kidney, predominatly in the glomeruli, where they can be detected by Congo red staining. Paraamyloidosis is more common in patients with light-chain myeloma proteins.

Diagnosis of multiple myeloma

Diagnosis of MM should be established by the following examinations [4]:

− Determination and assessment of the monoclonal (M-) componentby serum and/or urine protein electrophoresis; nephelometric quantification ofIgG, IgA and IgM immunoglobulins; characterisation of theheavy and light chains by immunofixation; and serum-freelight-chain measurement;

− Evaluation of BM plasma cell infiltration: BM aspiration and/or biopsies, which are the standard options to assess the number and characteristics. The BM sample should be used for FISH studies and also has the potential for immunophenotypic and molecular investigations;

− Evaluation of osteolytic lesions: a radiological skeletal survey, including spine, pelvis, skull, humeral and femoral bones, MRI and whole body CT. Fluorodeoxyglucose positron emission tomography is currently under evaluation but should not be systematically used;

− Complete blood cell count and biochemical analysis, with differential serum creatinine and calcium level.

The revised International Myeloma Working Group criteria for thediagnosis of MM include [14,15]:

Clonal BM plasma cells ≥10% or biopsy-proven bony or extramedullaryplasmacytoma;

Any one or more of the following myeloma defining events:

Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL);

Renal failure: creatinine clearance <40 mL per minute or serum creatinine >177 micromol/L (>2 mg/dL);

Anemia: hemoglobin value of >2 g/dL below the lower normal limits, or a hemoglobin value <10 g/dL;

Bone lesions: one or more osteolytic lesions on skeletal X-ray exam, CT, or positron emission tomography-CT;

Clonal bone marrow plasma cell percentage ≥60%;

Involved: uninvolved serum free light chain ratio ≥100 (involved free light chain level must be ≥100 mg/L);

>1 focal lesions.

The diagnosis of MM requires the presence of one or more MDE in addition to evidence of either 10% or more clonal plasma cells on BM examination or a biopsy-proven plasmacytoma. MDE consists of established CRAB (hypercalcemia, renal failure, anemia, or osteolytic lesions) features as well as 3 specific biomarkers: clonal bone marrow plasma cells ≥ 60%, serum involved / uninvolved free light chain ratio ≥ 100, provided the absolute level of the involved light chain ≥100 mg/L, and more than one focal lesion on MRI.

Staging of multiple myeloma

Salmon Durie Classification is still the most commonly used staging system [4,12,17].

Stage	***Criteria***
I	*All of the following:* Hemoglobin value > 100 g/l, Serum calcium value normal, On radiograph, normal bone structure or solitary bone plasmacytoma only, Low M-component production rates:

	IgG value < 50g/l,
	IgA value < 30 g/l,
	Urine light chain M-component on electrophoresis < 4g/24h
II	*Fitting neither stage I nor stage III*
III	*One or more of the following:*
	Hemoglobin value < 85 g/l,
	Serum calcium value > 12 mg/dl,
	Advanced lytic bone lesions,
	High M-component production rates:
	IgG value > 70g/l,
	IgA value > 50 g/l,
	Urine light chain M-component on Electrophoresis > 12g/24h.
Sub-classification:	A – Normal renal function,
	B – Abnormal renal function.

Combining b2-microglobulin with serum albumin and LDH has led to a Revised International Staging System (R-ISS) [4,16,17]:

IPI Group I b2-microglobulin <3.5 mg/l and serum albumin ≥ 3.5 g/dl,standard-risk chromosomal abnormalities by FISH, normal LDH,

IPI Group II b2-microglobulin <3.5 mg/l and serum albumin < 3.5 g/dl, or b2-microglobulin 3.5–5.5 mg/l,

IPI Group III b2-microglobulin >5.5 mg/l and either high-riskchromosomal abnormalities by FISH or high LDH.

The value of immunophenotyping and immunohistochemistry in diagnosing multiple myeloma

The immunochemical and immunophenotyping investigations are performed in order to determine the immunological type of MM *(Table 1)* and specific antigens on the surface of myeloma cells, which contribute to the identification of these cells and correlate with the diseaseevolution. Depending on the level of CD56 expression within the bone marrow, two

types of myeloma cells can be distinguished: the first – the immunephenotype CD138 +++, CD38 +++, CD19-, decreased expression CD40 and high expression CD56 +++, and the second – the immunephenotype CD138, CD38, CD40 andreduced CD56 + expression [12,18]. CD56 loss is associated with a more aggressive evolution of MM, which tends to spread myeloma cells to the peripheral blood. CD 28 is considered a marker of MM progression. CD28 level is higher in extramedullary relapses. Patients should be examined for the presence of M proteins via combined tests: a serum protein electrophoresis, serum immunofixation, and the serum free light chain assay [14,15]. Approximately, 2% of patients with multiple myeloma have a non-secretory disease, as well as no evidence of an M protein on any of the above mentioned studies.

Table 1

Immunochemical classification of multiple myeloma

Immunologic type	Frequency, %
IgG myeloma	55-65
Ig A myeloma	20-25
IgD myeloma	2-5
IgM myeloma	0.5
IgE myeloma	< 0.1
Bence-Jones myeloma	12-20
Non-secretory myeloma	1-4
Biclonal myeloma	1-2

The value of cytogenetic and molecular examinations in diagnosing multiple myeloma

BM examinations at the time of initial diagnosis should include FISH, designed to detect t(11;14), t(4;14), t(14;16), t(6;14), t(14;20), trisomies, and del(17p) [4,14,15]. Conventional karyotyping has a value to detect hypodiploidy and deletion 13, however, if FISH studies are carried out, additional value of the initial risk-stratification is limited. On FISH studies of the BM, approximately 40% of MM cases are

characterized by the presence of trisomies in the neoplastic plasma cells (trisomic MM), while most of the rest have a translocation involving the IgH locus on chromosome 14q32 (IgH translocated MM). A small rate of patients have both trisomies and IgH translocations. Trisomies and IgH translocations are considered primary cytogenetic abnormalities and occur at the time of MGUS onset. Other cytogenetic changes, termed as secondary cytogenetic abnormalities may arise along withMM, including gain (1q), del (1p), del(17p), del(13), RAS mutations, and secondary translocations involving MYC. Both primary and secondary cytogenetic abnormalities can influence the evolution, therapeutic response and prognosis of the disease. Gene expression profile, if available, may provide additional prognostic value.

The value of radiological imaging in diagnosing multiple myeloma

A radiological skeletal survey, including spine, pelvis, skull, humeral and femoral bones is required. MRI or CT scan may be needed to evaluate symptomatic bone sites, even though the skeletal survey is negative and the patient has symptoms suggesting bone lesions [4,14,15]. The extent of bone disease is best assessed by low-dose whole body CT *(Table 2)* [15,19]. MRI imaging is useful in assessing extramedullary, suspected cord compression, or when a detailed imaging of a specific symptomatic area is required. MRI scans mayalso help to identify focal BM lesions in patients with suspected smoldering MM, which can be observed before true osteolytic disease occurs. Conventional skeletal survey is less sensitive than low-dose whole body CT and is recommended only if more advanced imaging techniques are not available.

Table 2

Classification of multiple myeloma according to the bone and extramedullary site involvement

Type of the bone and extramedullary involvement	Frequency, %
Diffuse with foci	60
Diffuse	24
Multiple foci	15
Sclerosing	< 1
Predominantly visceral	< 0,5

Differential diagnosis of multiple myeloma

The differential diagnosis of MM is carried out along with other diseases that may develop with bone marrow plasmacytosis, osteolytic foci on imaging examination, hyperproteinemia and porteinuria [2,12,13,15,18]:

Neoplastic:
MGUS,
solitary plasmacytoma,
Waldenström macroglobulinaemia,
non-Hodgkin lymphoma,
chronic lymphocytic leukaemia,
primary amyloidosis,
heavy-chain disease;

Non-neoplastic:
chronic cold haemagglutinin disease,
transient (e.g. along with infections),
HIV infection,
Gaucher's disease.

MGUS shows a higher prevalence in individuals over 50 (3.2%) and 70 (5.8%) years old [2,15]. It is characterized by the presence of a serum M-protein (<30 g/L) and less than 10% plasma cells in the BM with no evidence of other B-cell lymphoproliferative disorders and no

symptoms of organ or tissue impairment due to the monoclonal gammopathy. The transformation rate to MM is about 1% per year, with an actuarial probability of malignant evolution of 30% at 25 years of follow-up. The main factors associated with MGUS progression include M-protein size, IgA isotype, abnormal free light-chain ratio, rising M-protein during the first years of follow-up, and the presence of more than 95% phenotypically aberrant plasma cells within the BM cellularity.

The presence of a solitary plasmacytoma has been recognized in up to 3% of patients with a plasma cell disorders, commonly on the vertebral column [2,15]. The diagnostic criteria require the existence of a solitary plasma cell tumor in which the biopsy confirms plasma cell histopathology, a negative skeletal survey and absence of plasma cell infiltration in a random BM sample (<10%), as well as no evidence of anaemia, hypercalcaemia or renal impairment. Patients should undergo a review of the diagnosis, if a paraprotein persists after the eradication of plasmacytoma with local treatment.

Waldenström macroglobulinaemia is a B-cell neoplasm with BM involvement and an IgM monoclonal gammopathy of any concentration [2,13]. It is composed of small lymphocytes, plasmacytoid lymphocytes and plasma cells, usually involving the BM and sometimes lymph nodes and spleen. Waldenströmmacroglobulinaemia does not fulfil the criteria for any other B-cell neoplasm which may have plasmacytic differentiation. The detection of a paraprotein is common. Next-generations have identified activating mutations of MYD88 in 90–100% of cases and CXCR4 in 28% of cases. These findings may be useful in the differential diagnosis of the disease.

Principles of management and treatment options in multiple myeloma

The management of MM has been developed according to the principle of a customized approach for each patients. Specialized literature data have reported that cases of asymptomatic (latent) myeloma do not

require immediate treatment. Current treatment programs and protocols may increase the patient's survival beyond 5 years in up to 50% of patients under 75 years [7]. In 3 - 20% of MM cases, a complete remission under the complex treatment can last for many years. It is recommended to initiate the treatment in all patients with active MM (symptomatic), who fit the CRAB criteria (hypercalcemia > 11.0 mg/dL, creatinine >2 mg/ml, anemia with Hb<10 g/dL and / or active bone lesions). The treatment of MM is combined, whereas the treatment approach should be determined while considering the pain syndrome, hyperproteinemia and degree of hyperviscosity, renal failure, hypercalcemia, spinal cord compression, the presence of osteolytic lesions and pathological fractures.

Different chemotherapy regimens are applied to suppress and eradicate the malignant cell clone [4,12,16,18,20].

MP regimen (Melphalan + Prednisolone) in prolonged or intensive form is recommended for patients, who don't fit the criteria for HSCT .

Extended MP scheme:

Melphalan, 10 mg orally daily or over a day until leukopenia and thrombocytopenia develop, up to a summary dose of 200-250 mg +Prednisolone within the first 7-10 days, 60 mg orally daily, then subsequently reducing the dose by 5 mg /day to a daily dose of 15 mg, which is maintained until the end of the treatment course.

Intensive MP scheme:

Melphalan, 9 mg/m^2 orally for 4 days + Prednisolone 1-2 mg/kg orally forover 4 days, by reducing thedose on day 5 and the suspension on day 9. The interval between these treatment cycles is 4-6 weeks.

Extended CP scheme:

Cyclophosphamide, 400 mg intravenously daily over a day up to the summary dose of 8-10 g. + Prednisolone (see the prolonged MP regimen).

Intensive CP scheme:

Cyclophosphamide, 400 mg intravenously daily for 4 days with 3-4 weekintervals + Prednisolone (see the intensive MP regimen).

Cyclophosphamide is a priority drug in cases of renal failure, with tendency to leukopenia and thrombocytopenia, since it has a less marked and less stable hemodepression action as compared to Melphalan.

Melphalan is mainly eliminated via the kidneys and can be accumulated in patients with renal failure, thus causing a hemodepression.

At the same time, the cardiotoxicity and hepatotoxicity of cyclophosphamide is higher as compared to melphalan. Cyclophosphamide can cause bleeding cystitis.

Most international clinical guidelines and protocols,the standard treatment includes high dose of Melphalan (200 mg/m2), followed by the autologous HSCT in patients aged under 65 years without severe comorbidities [7].

MP and CP regimens are more frequently used in stage I. Different combined chemotherapy regimens have been recommneded for stage II and III MM: VMCP (Vincristine, Melphalan, Cyclophosphamide, Prednisolone), VBAP (Vincristine, Carmustine, Adriablastine, Prednisolone), VBMCP or M-2 (Vincristine, Carmustine, Melphalan, Cyclophosphamide, Prednisolone), ABCM (Adriablastine, Carmustine, Cyclophosphamide, Melphalan), VAD (Vincristine, Adriablastine, Dexamethasone).

It has been considered that a combined chemotherapy should be indicated in the newly-diagnosed patients with unfavorable prognostic factors, in cases of relapsed MM and secondary resistance to the MP protocol.

One of the mostly used combined chemotherapy regimens is VAD regimen: Vincristine 0.2 mg/m^2 intravenously on days 1-4 + Adriablastine 9 mg/m^2 intravenously on days 1-4 + Dexamethasone 20 mg/m2 orally on days 1-4, 9-12, 17-20. VAD cycles are repeated every 28 days from the first day of the previous cycle. The VAD regimen is indicated more frequently in MM with aggressive evolution and in patients with renal impairment. In cases of renal impairment, the doses

of the drugs in the VAD regimen are not reduced. As a rule, at least 6-12 cycles of combined chemotherapy are required.

Other chemotherapy regimens are currently being used [2,3,12,16]:

Bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11 with the interval of 22 days –8 cycles can totally be performed.

Long-lasting regimen with Thalidomide 100 mg orally daily.

BP: Bendamustine 60-100mg/m^2intravenously on days 1, 2 + Prednisolone 1mg/kg orally on days 1-4, with an interval of 29 days.

BVD: Bendamustine 70 mg/m^2intravenously on days 1, 4 or days 1, 8 + Bortezomib 1.3mg/m^2intravenously on days 1, 4, 8, 11 (or on days 1, 8, 15, 22), with an interval of 29 days.

Lenalidomide + Dexamethasone: Lenalidomide 25mg/m^2orally for 21 days.

Dexamethasone 40mg/m^2orally on days 1-4, 9-12, 17-20, with an interval of 29 days.

PAD (VAD with Bortezomib): Bortezomib 1.3 mg/m^2 intravenously on days 1, 4, 8 and 11 + Doxorubicin 9 mg/m^2 on days 1-4 + Dexamethasone 40 mg intravenously on days 1-4 and 8-11, with an interval of 22 days.

RVD: Lenalidomide 15 mg orally on days 1-14 + Bortezomib 1.0 mg/m2 intravenously on days 1, 4, 8, 11 + Dexamethasone on 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, 12, with an interval of 22 days – first 4 courses; the following 5-8 courses: Lenalidomide 15 mg orally on days 1-14 + Bortezomib 1.0 mg/m^2 intravenously on days 1, 4, 8, 11 + Dexamethasone 20 mg orally on days 1, 2, 4, 5, 8, 9, 11, 12, with an interval of 22 days.

VCD: Bortezomib 1.3 mg/m^2intravenously on days 1, 4, 8 and 11 + Cyclophosphamide 400 mg intravenously on days 1, 4, 8, 11 or 50 mg orally on days 1-14 + Dexamethasone 40mg intravenously on days 1-4 and8-11.

VMP: Melphalan 9mg/m^2orally on 1-4 days + Prednisolone 60mg /m^2orally on 1-4 days + Bortezomib 1.3mg/m^2intravenously (bolus) on days 1, 4, 8, 11, 22, 25, 29, 32 with a43-days interval between cycles. 9

cycles should totally be performed. Bortezomibshould be administered on days 1, 8, 22, 29 during cycles 5-9.

VTD: Bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11 + Thalidomide 50 mg orally daily on days 1-14 (if tolerated, the dose may later be increased to 100 mg daily on days 15-28) + Dexamethasone 40 mg orally on days 1, 2, 3, 4, 8, 9, 10 and 11. Cycle duration – 28 days.

Bortezomib in combination with pegylated liposomal Doxorubicin: Bortezomib 1.3 mg/m^2x 2 times weekly for 2 weeks on days 1, 4, 8, 11 + pegylated liposomal Doxorubicin 30mg/m^2 on day 4, administered after Bortezomib injection, with an interval of 21 days. Up to 8 cycles can be administered. Dexamethasone may be combined orally at a dose of 20 mg on days 1, 2, 4, 5, 8, 9, 11, 12.

In patients under 65 years, the high-dose chemotherapy and autologous HSCT may be performed [11]. A double HSCT may be used in cases of relapses. In cases of the autologous HSCT failure, the allogen HSCT should be performed.

Prednisolone is a compulsory component of the treatment of MM at the dose of 15-20 mg daily. It reduces osteolysis by inhibiting the activating factor of osteoclastic cells. Prednisolone is also efficient in cases of hypercalcemia. High-dose corticosteroids are used as a standalone treatment option, which is very important due to a possibility of MM management in patients with myelosuppression. Treatment regimen comprises high dose Dexamethasone 20 mg/m^2 daily on days 1-4, 9-12, 17-20, with an interval of 35 days. This drug has a cytolytic effect and provides a response in 25-30% of patients.

Local radiotherapy is indicated:

- in all cases with the risk of pathological fractures, even in cases when the pain syndrome is absent;
- onthe tumor sites located in the bones and soft tissues;
- in cases ofradiculoalgiadue to the spinal nerve root compression by tumor accretion.

The generalization of MM cannot serve as an argument for not applying local radiotherapy. In advanced, relapsed and refractory cases,

or resistant to chemotherapy, local radiotherapy is the only helpful and efficient treatment option. The conventional summary dose on the tumor site may be up to 50 Gy.

In order to combat and prevent the complications caused by the protein pathology syndrome, plasmapheresis is performed until the normalization of total protein.

Red cell concentrate transfusions may be needed to reduce the anemic syndrome, which exert negative impact on ECOG-WHO score, especially in the elderly and in patients with cardiovascular diseases.

Recombinant erythropoietins are also used for this purpose, providing a high response.

After the completion of the first-line treatment, the maintenance therapy should be performed within 2 years.

The selection of therapy for recurrent or refractory MM depends on several parameters, such as age, ECOG-WHO score, comorbidities, efficiency and tolerability of previous treatment, number of previous treatment lines, available treatment options and time since last dating. The following chemotherapy regimens may be used: Daratumumab, Daratumumab + Bortezomib + Dexamethasone, Daratumumab + Lenalidomide + Dexamethasone, Pomalidomide + Dexamethasone, Pomalidomide + Bortezomib + Dexamethasone, Elotuzumab + Lenalidomide + Dexamethasone + Carfilzomib, Ixazomib + Lenalidomide + Dexamethasone, Panobinostat + Bortezomib + Dexamethasone.

A second autologous HSCT may be performed in young patients, if they favorably responded to the previous HSCT and had a PFS for more than 24 months.

Evolution and prognosis

The evolution of MM varies. Once the diagnosis is established, the evolution depends on the response to treatment. The proper evaluation of prognosis requires a multifactorial assessment. OS in multiple myeloma is affected by host characteristics, tumor burden (stage), biology (cytogenetic aberrations), and response to therapy [14,15]. Tumor

burden in MM has traditionally been estimated using the Durie-Salmon Staging and the International staging system (ISS). Disease biology best reflected based on the molecular subtype of MM, the presence or absence of secondary cytogenetic abnormalities such as del (17p), gain (1q), or del (1p). In addition to cytogenetic risk factors, two other markers are associated with aggressive disease biology: the elevated serum lactate dehydrogenase and evidence of circulating plasma cells on routine peripheral smear examination (plasma cell leukemia).

The survival of untreated patients accounts for approximately 7 months. The average survival is 30 months under the treatment, ranging from a few months to 10-15 years [12]. The results from randomized controlled trials using modern chemotherapy reveal that the median survival in MM is approximately 6 years [14,15]. In the subgroup of patients eligible for autologous HSCT, 4-year survival rates exceed 80%; the median OS among these patients is approximately 8 years. Among the elderly patients (age >75 years), median OS is lower, and is approximately 5 years[21].The prognosis of the disease remains unfavourable in most cases, especially with generalized stages.

Clinical case studies

Clinical case 1

Patient K., 64 years old, complains of fatigue, nausea, vomiting, and pain in the thorax.

The patient has been considered ill for 3 months since an increasing fatigue and pain in the thorax have appeared. The vomiting occurred 2 weeks ago.

Clinical findings: Severe condition of the patient. Nourishment is decreased. Skin is pale and dry. Tongue is dry. Peripheral lymph nodes are not palpable. Respiration is vesicular. Heart sounds are quiet. Pulse rate is 96 beats/min. Blood pressure is 145/95 mm/Hg. Abdomen is painless at palpation. Liver and spleen are not enlarged. Stool is regular, of typical colour. Diuresis – 600 ml/24 hours.

Blood findings: Hb – 75 g/l, erythrocyte count – $1{,}9x10^{12}$/l, thrombocyte count – 40‰, leukocyte count – $7{,}2x10^{9}$/l, band forms – 6%, segm. – 60%, eos. – 4%, lymph. – 24%, mon. – 6%, erythrocyte sedimentation rate – 76 mm/ hour.

Biochemical analysis of the blood: total protein level 120 g/l, urea 21 mmol/l.

Skeletal CT scan: Diffuse osteoporosis of the spinal column and ribs. Pathologic fractures inT1-T3vertebrae.

1. What diagnosis would you establish for this case?
2. Could you develop the patient's investigation and treatmentplan?

Clinical case 2

Patient T., 73 years old, presented with fatigue, dizziness and lumbar pain.

The increasing lumbar pain had appeared 6 months ago. The fatigue and the dizziness developed gradually. A week ago the patient had mentioned a crunch and intensification of pain syndrome in the lumbar part of spinal column after blunt moving.

Clinical findings: Severe condition of the patient. Forced patient's position. The functions of lower extremities are maintained. Skin is pale. Vesicular respiration. Cardiac sounds are quiet. Apical systolic murmur is detectable. Pulse rate is 88 beats/min. The pulse is full. Blood pressure is 130/85 mm/Hg. Abdomen is soft and painless on palpation. Liver and spleen are not palpable. The functions of pelvic organs are safe.

Blood findings: Hb – 70 g/l, erythrocyte count – $1,9x10^{12}$/l, leukocyte count – $4,5x10^{9}$/l, band forms. – 4%, segm. – 66%, lymph. – 25%, mon. – 5%, erythrocyte sedimentation rate – 72 mm/h.

Biochemical analysis of the blood: total protein level 104 g/l.

Radiological skeletal survey: Diffuse osteoporosis of the spinal column and skull. Pathologic fractures in L1-L2 vertebrae.

1. What diagnosis would you establish for this case?
2. Could you develop the patient's investigation and treatmentplan?

Control tests

S The cause of bone destruction in multiple myeloma is:

A. increased blood viscosity
B. appearance of cryoglobulins
C. decrease in blood Ca
D. paraproteinemia
E. the action of osteoclast-activating factor
Correct answer: **E**

S Which of the following statements is true in diagnosing polycythemia vera:

A. the skin becomes gradually reddish
B. venous and arterial thrombosis may sometimes be the initial manifestations of the disease
C. skin itching after being exposed to water
D. infectious complications are the cause of death
E. bone marrow examination shows hyperplasia and marked increase of megacaryocytes
Correct answer: **D**

S In multiple myeloma, the increased blood viscosity is manifested clinically by:

A. headache
B. dizziness
C. paresthesia
D. somnolence
E. all above-mentioned signs
Correct answer: **E**

S The first-line treatment option in multiple myeloma associated with renal failure is as following:

A. Chlorambucil
B. Melphalan
C. Busulfan

D. Cyclophosphamide
E. Vincristine
Correct answer: **D**

S In multiple myeloma, the morphological substrate of the tumor is composed of:
A. blast cells
B. mature lymphocytes
C. malignant plasmatic cells
D. myeloid cells at the different stages of maturation
E. monocytes
Correct answer: **C**

S The diagnosis of multiple myeloma is definitelyconfirmed by the:
A. peripheral blood count
B. x-ray examination of the bones
C. urinalysis
D. biochemical analysis of the blood
E. bone marrow aspiration with determination of blast cells
Correct answer: **E**

S Which of the following statement is true in diagnosing multiple myeloma:
A. bone pain
B. fatigue, dizziness, sometimesdrowsiness
C. mandatory bleeding syndrome
D. tumors may develop in different bone sites ofthe skeletal system
E. compression fractures of the vertebrae may occur
Correct answer: **C**

S Which of the following drugs may be used to reduce hypercalcemia:
A. Bonefos
B. Cyclophosphamide
C. Melphalan

D. Vincristine
E. Plasmapheresis
Correct answer: **A**

S The following treatment option is used in order to inhibit osteoclast activating factor aimed at reducing osteolysis:
A. Cyclophosphamide
B. Melphalan
C. Radiotherapy
D. Prednisolone
E. Plasmapheresis
Correct answer: **D**

S Multiple myelomadevelopment is associated with mutation at the level of:
A. pluripotent stem cell;
B. the predecessors of myelopoiesis;
C. the predecessors of lymphopoiesis;
D. predecessors of lymphocytes-B;
E. blast cells
Correct answer: **D**

S The most common variant of immunochemical assay for multiple myeloma is:
A. immunoassay with IgA
B. immunoassay with IgD
C. immunoassay with IgG
D. immunoassay with IgE
E. immunoassay with IgM
Correct answer: **C**

S In case of suspected multiple myeloma case, an important criterion is:
A. the sequence of damage to the lymph nodes;
B. weight loss;
C. fever;

D. pain in bone associated with anemia;
E. hemorrhagic syndrome
Correct answer: **D**

S Multiple myeloma develops more commonly in persons aged:
A. < 20 years
B. > 20 years
C. 40-70 years
D. < 30 years
E. 20-30 years
Correct answer: **C**

S In the treatment of multiple myeloma not associated with myelonomic nephropathy, the medication of choice is:
A. Melphalan
B. Mileran
C. Hydrea
D. Leukeran
E. Vincristine
Correct answer: **A**

S The clinical picture of multiple myeloma includes the following with an exception of:
A. clinical symptoms caused by the destruction of bones;
B. hypercalcemia;
C. lymphadenopathy is very rare;
D. development of para-amyloidosis;
E. splenomegaly and hepatomegaly are mandatory
*Correct answer***: E**

S Which of the following statements on multiple myeloma is true:
A. it commonly occurs in young people;
B. sudden onset and fast evolution;
C. peripheral lymph nodes frequently are increased;
D. there are no characteristic infectious complications;

E. a positive diagnosis is confirmed only by the morphological examination of the bone marrow punctate in which plasma cells are detected

Correct answer: **E**

S In patients with multiple myeloma with tendency to leukopenia and thrombocytopenia the prior monochemotherapy is:

A. Cyclophosphamide
B. Melphalan
C. Vincristine
D. Adriablastin
E. Prednisolon

Correct answer: **E**

S In multiple myeloma the destruction of bones occurs mainly in:

A. the forearm bones;
B. the lumbar vertebrae;
C. the humerus;
D. the femoral bones
E. the bones of the calves

Correct answer: **B**

S The diagnosis of solitary plasmacytoma is carried out on the basis of:

A. sternal puncture;
B. cytological or histological investigation of the tumour;
C. trepanobiopsy of the iliac bone;
D. the presence of plasmacytes in the peripheral blood;
E. biochemical blood analysis

Correct answer: **B**

S The clinical picture of solitary myeloma is characterized by:

A. paraproteinemic syndrome;
B. hemorrhagic syndrome;
C. osteomedullary syndrome;
D. anemic syndrome;

E. clinical signs are determined by the localization of the tumour
Correct answer: **E**

C In multiple myeloma, osteodestruction most commonly affects:

A. the distal parts of the femoral bone;
B. the vertebrae with the development of compression fractures;
C. the ribs with pathologic fractures;
D. the distal parts of the humeral bones;
E. the forearm bones
*Correct answer***: B, C**

C The diagnosis of multiple myeloma is confirmed when the sternal aspiration reveals the infiltration with plasma cells:

A. exceeding 10% in cases with osteodestruction;
B. exceeding 5% and osteodestruction is present;
C. exceeding 20% in absence of osteodestruction;
D. accounting for 15% in absence of osteodestruction;
E. exceeding 10% in absence of osteodestruction
*Correct answer***: A, C**

C The development of myelomic nephropathy is caused by:

A. hyperparaproteinemia;
B. nephrolithiasis;
C. hematuria;
D. hyperviscosity;
E. hydronephrosis
Correct answer: **A, D**

C Which of the following statements about solitary plasmacytoma is true:

A. it develops from lymphoid cells located extramedulary;
B. it develops from plasmocytic cells located extramedulary;
C. first it affects the bone marrow;

D. severe osteodestructive process;
E. the tumor focus is located extramedulary
Correct answer: **B, E**

C Multiple myeloma may be diagnosed if associated with the following criteria:

A. Over 15% of myeloma cells in the bone marrow aspirate
B. Osteolytic lesions on X-ray examination of the bones
C. Detection of pathologic paraprotein
D. Proteinuria
E. Anemia and accelerated ESR in the peripheral blood count
*Correct answer***: A, B**

C Which of the following examinations are mandatory to confirm the diagnosis and determine the stage of multiple myeloma:

A. X-ray examination of the bone skeleton
B. Plasma proteins electrophoresis
C. Coagulation tests
D. Determination of bilirubin and aminotransferases concentrations
E. Neciporenco urine test
Correct answer: **A, B**

C Which of the following immune disorders may occur in multiple myeloma:

A. Monoclonal gammapathy
B. Failure of antibodies synthesis
C. Underproduction of normal plasmatic cells
D. Frequent infectious complications
E. Delayed hyperesensibility reaction
Correct answer: **A, B, C, D**

C The following examinations are applied to diagnose the solitary myeloma:

- **A.** X-ray examination of the tumor
- **B.** Biopsy and morphological examination of the tumor
- **C.** Ultrasound scanning
- **D.** Bone marrow aspiration
- **E.** Computerized tomography

Correct answer: **B, D**

C In multiple myeloma the genesis of anemia constitutes:

- **A.** Iron deficiency
- **B.** Hemolysis
- **C.** Aplasia
- **D.** Metaplasia
- **E.** Chronic renal failure

Correct answer: **D, E**

C The most frequent complications of multiple myeloma are the following:

- **A.** Hemolytic crisis
- **B.** Hepatosplenomegaly
- **C.** Paraproteinemic coma
- **D.** Gingival hyperplasia
- **E.** Peripheral sensorial neuropathy

Correct answer: **C, E**

C In multiple myeloma the development of chronic renal failure depends on:

- **A.** Percentage of myeloma cells in the bone marrow aspirate
- **B.** Hyperparaproteinemia
- **C.** Anemia
- **D.** Hypercalcemia
- **E.** Blood hyperviscosity

Correct answer: **B, D, E**

C Which of the following statements are not true for the diagnosis of multiple myeloma:

- **A.** The disease develops in the elderly
- **B.** The disease slowly develops
- **C.** Paramyloidosis never occurs
- **D.** Leukemic conversion is not possible
- **E.** Tumor manifestations do not occur

Correct answer: **C, D, E**

C There are the following clinical manifestations of paramyloidosis in multiple myeloma:

- **A.** Bone fractures
- **B.** Macroglossia
- **C.** Various dermatoses
- **D.** Loss of orientation
- **E.** Gastrointestinal disorders

Correct answer: **B, C, E**

C In multiple myeloma hypercalcemia is manifested by:

- **A.** Nausea, vomiting
- **B.** Somnolence
- **C.** Loss of orientation
- **D.** Presence of M-gradient
- **E.** Infectious complications

Correct answer: **A, B, C**

C Which of the following signs suggest for stage I multiple myeloma:

- **A.** Marked osteolytic lesions
- **B.** Hemoglobin over 100 g/l
- **C.** Normal plasma Ca concentration
- **D.** Absence of osteolytic lesions or one osteolytic focus
- **E.** Concentration of M-component: Ig G < 50 g/l, Ig A < 30 g/l, protein Bence-Jones in urine < 4 gr/24 ore

Correct answer: **B, C, D, E**

C Which of the following signs suggest stage III multiple myeloma:

- **A.** Hemoglobin less than 85 g/l
- **B.** Normal plasma Ca concentration
- **C.** Marked osteolytic lesions
- **D.** Concentration of M-component: Ig G > 70 g/l, Ig A > 50 g/l, protein Bence-Jones in the urine > 12 gr/24 ore
- **E.** Plasma Ca concentration > 12 mg/100 ml

Correct answer: **A, C, D, E**

C In multiple myeloma renal failure is caused by:

- **A.** Reabsorption of protein Bence-Jones
- **B.** Canalicular precipitation of micromolecular protein
- **C.** Development of contracted kidney
- **D.** Renal lithiasis
- **E.** Intrarenal hydronephrosis

Correct answer: **A, B, C, E**

C The treatment of generalized multiple myeloma comprises:

- **A.** Prolonged chemotherapy
- **B.** Intensive high-dose chemotherapy
- **C.** Radiotherapy
- **D.** Glucocorticoid therapy
- **E.** Physiotherapy

Correct answer: **A, B, C, D**

C In multiple myeloma, pathologic protein syndrome is manifested by:

- **A.** Hypercalcemia
- **B.** Hyperparaproteinemia
- **C.** Proteinuria
- **D.** Uremia
- **E.** Peripheral microcirculation disorders

Correct answer: **B, C, D, E**

C Which of the following pathologies should be differentiated from multiple myeloma, if consifering the possibility of reactive plasmocytosis:

A. Polycythemia vera
B. Chronic hepatitis
C. Cancer
D. Immune complex diseases
E. Agranulocytosis
Correct answer: **B, C, D, E**

C The diagnosis of multiple myeloma is confirmed by the presence of the following syndromes:

A. Intoxication syndrome
B. Plethoric syndrome
C. Osteomedullary syndrome
D. Hemolytic syndrome
E. Pathologoproteinic syndrome
*Correct answer:*C, E

C In multiple myeloma, the classic Khaler triad is manifested by:

A. pain towards the damaged bones;
B. paraparesis;
C. local swelling;
D. pathological bone fractures;
E. hyperviscosity
*Correct answer:*A, C, D

C The most common clinical anatomical forms of multiple myeloma are:

A. predominant visceral form;
B. diffuse form with foci;
C. diffuse form;
D. sclerosing form;
E. a form with multiple foci
Correct answer: **B, C, E**

C The following immunochemical forms occur more commonly in multiple myeloma:

A. myeloma G;
B. myeloma E;
C. Bence-Jones myeloma;
D. myeloma M;
E. myeloma A
*Correct answer:***A, C, E**

C Multiple myeloma is characterized by:

A. clinical symptoms caused by bone damage;
B. development of paraamyeloidosis;
C. hypercalcemia;
D. hepatomegaly and splenomegaly are mandatory;
E. lymphadenopathy is very rare
*Correct answer:***A, B, C, E**

C Which of the following statements regarding multiple myeloma is true:

A. Painful bones are one of the initial clinical signs;
B. Lymphadenopathy is very rare;
C. It frequently develops in young people;
D. People aged 40-70 are more commonly affected;
E. Infectious complications often occur
Correct answer: **A, B, D, E**

C Choose the examinations required for patients diagnosed with multiple myeloma, confirmed morphologically:

A. bone x-ray;
B. assessment of total protein and calcium levels in serum;
C. determining the type of immunoglobulin monoclonal in serum;
D. cytochemical reaction on non-specific esterase;
E. complete blood count and complete urinalysis
*Correct answer:***A, B, C, E**

C Patients with multiple myeloma are treated via:

A. chemotherapy;
B. radiotherapy;
C. bisphosphonates;
D. plasmapheresis;
E. iron therapy

*Correct answer:***A, B, C, D**

C In multiple myeloma, the following laboratory tests are required:

A. general protein test;
B. calcium concentration in serum;
C. serum iron test;
D. urea test;
E. creatinine test.

Correct answer: **A, B, D, E**

C In patients with multiple myeloma, the peripheral blood analysis might detect:

A. anemia;
B. thrombocytopenia;
C. leukopenia;
D. increased erythrocyte sedimentation rate;
E. hyperchromia of erythrocytes.

Correct answer: **A, B, C, D**

C Which of the following statements regarding solitary myeloma is false:

A. The focus of tumor is located extramedulary;
B. The bone marrow is first involved;
C. Marked process of bone destruction;
D. Anemia, leukopenia, thrombocytopenia develop;
E. Sensory polyneuropathy develops.

*Correct answer:***B, C, D, E**

C Choose the medications used in the treatment of multiple myeloma:

- **A.** Cyclophosphamide
- **B.** Mileran
- **C.** Melphalan
- **D.** Bondronat
- **E.** Prednisolone

Correct answer: **A, C, D, E**

C Which of the following statements related to solitary plasmacytoma is true:

- **A.** The bone marrow is affected first;
- **B.** The tumor is located extramedulary;
- **C.** It develops from plasmocytes located extramedulary;
- **D.** Its clinical signs are determined by the localization of the tumour;
- **E.** The diagnosis of solitary plasmacytoma is confirmed by cytological or histological examination of the tumourvia the detection of malignant plasma cells

Correct answer: **B, C, D, E**

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