FOLIA 215

Annales Universitatis Paedagogicae Cracoviensis

Studia ad Didacticam Biologiae Pertinentia VI (2016)
ISSN 2083-7267

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# Multiple myeloma – cancer among elderly people

## Epidemiology and etiopathogenesis of multiple myeloma

Multiple myeloma is the second most common hematological cancer. This represents 1–2% of all malignant tumors and 12–15% of hematologic malignancies occurring in humans. Morbidity level in Europe is 4–6/100,000 cases per year. It is rated that every year in Poland we have about 1,500 new cases of multiple myeloma and unfortunately the number is growing every year. Multiple myeloma occurs more often (about one and a half time) in men than in women, and two times more often in black people than in caucasian people. It does not occur in children and rarely in people below 30 years of age. Majority of cases (90%) occur in people over 50 years of age and the median age at the time of diagnosis is 65–70 years (Becker, 2011; Dmoszyńska et al., 2011; Jamroziak, 2013).

Plasmacyte growth is the consequence of lymphocyte B differentiation, which mainly occurs in the lymph nodes. The process of line B cells growth can be divided into two stages: "antigen independent" and "antigen dependent" (Klein et al., 2011).

Stage one of lymphocyte B growth takes place in bone marrow, where immunoglobulin gene rearrangements occur – initially heavy chain, and then light chain. Cells shift towards line B and after next stages they ripen to B cells characterized by the present of surface immunoglobulin class IgM kappa or IgM lambda. Cells escape from the bone marrow and start to migrate to multiplication centers in peripheral lymphoid organs – including lymph nodes. B lymphocytes flow to them with blood. After passing into the node, B lymphocytes contact Th lymphocytes, which results in forming of multiplication center known as lymphocytic clump (follicle). This is followed by selection of high affinity immunoglobulin B cells and differentiation of memory B cells (CD20+, CD19+, CD27+, CD38–) and early plasma cells (CD20–, CD19+, CD27++, CD38++) – antigen dependent stage. Differentiation of B cells into plasma cells and memory cells requires serious molecular changes, somatic hypermutation (SHM) and class switch recombination (CSR) (Klein et al., 2011; Beason et al., 2012; Jamroziak, Warzocha, 2015).

Taking into account the clinical symptoms of multiple myeloma, two premalignant variants can be considered, monoclonal gammapathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). Also Waldenstrom Macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma-proliferative disorder, skin changes) and amyloidosis, which is a disease that occurs when abnormal protein is deposited in our organs, are all places under monoclonal gammapathy. A common feature of these units is the presence of monoclonal protein in serum and/or urine, or the presence of amyloid deposits in various organs (Walewski, 2011; Beason et al., 2012).

The initial stage of the disease is probably the consequence of chronic antigenic stimulation associated with infections, chronic diseases or exposure to chemical carcinogens and radiation, and consists in the creation of numerous mild plasma clones (Jamroziak, 2013).

MGUS is detected in 3–4% of people aged >50 years, and 5% of people aged >70 years, more often in men. Transformation into more aggressive lymphoproliferative diseases appears to be related with the type of monoclonal protein. Majority of MGUS cases related with the production of IgM is associated with progression to Waldenstrom Macroglobulinemia, and clinical cases associated with the presence of IgA and IgG most often transform to MM, moreover, an MGUS is associated with the presence of light chains. Patients with MGUS do not have any symptoms of organ damage resulting from proliferation of plasma cells (Dmoszyńska et al., 2015; Surowiec et al., 2016).

Smoldering multiple myeloma (SMM), which is an intermediate state between MGUS and advanced stage multiple myeloma, occurs in about 8% of patients in whom the contents of plasma cells in the bone marrow is usually 10–20%, and median of M protein concentration in serum ~3g/dl. More than 90% of the cases has hypogammaglobulinaemia and about 70% of patients have present monoclonal light chains in urine. The risk of developing symptomatic multiple myeloma in these patients is 10% during the first 7 years, and then decreases. As in the case of MGUS, patients with asymptomatic myeloma don't have any symptoms of organ damage, whereas the concentration of monoclonal protein or percentage of plasma cells in the biopsy tissue is higher.

Smoldering myeloma is a heterogeneous group of conditions, from which in some patients quickly, usually within two years, develops symptomatic myeloma, and in a group of patients asymptomatic state will be present for years (Dmoszyńska et al., 2015).

The risk of progression to symptomatic myeloma from the moment of diagnosis of smoldering multiple myeloma is not clear. There have been distinguished several parameters helpful in predicting the risk of disease exacerbating. They are: protein M level (o ≥3 g/dl and/or 10% to 60%), plasma cell percentage in bone marrow, percentage of abnormal plasma cells and presence of free light chains (FLC), lack of expression of heavy light chain (HLC), magnetic resonance disorders (MRI), cytogenetic abnormalities, of IgA isotope and Bencea's Jones proteinuria (Gao et al., 2015).

In addition to the typical form of MM with bone marrow sclerosis there are also rare, localized variants – isolated osseous and extraosseous plasma tumor. Diagnosis is made based on the presence of clonal plasma cells in the tissue biopsy from a single tumor, and by exclusion of other places infiltrated by myeloma. Additionally, we recognize negativly prognosin plasma cell leukemia which is characterized by the presence of plasma cells circulating in the peripheral blood, in the quantity of more than 2x 109/L or/and constituting at least 20% of blood cells (Jamroziak et al., 2013).

In borderline cases, the basis for differentiating between PCM and MGUS may be immunophenotype evaluation.

Healthy plasma cells have immunophenotype: CD38+, CD138+, CD19+, CD45+, CD56– (Jamroziak, Iskierka-Jażdżewska, 2015).

Typical myeloma phenotype is sIg–, CD20–, CD19– (90%), CD38+, CD45– (99%), CD138+, CD56+ (70%). The active form of MM, only in exceptional cases has no malignant phenotype. The elements that differ from the normal plasma cells is usually a reduced expression of CD19 and CD45, as well as increased expression of CD56 and CD138. Differentiation of malignant phenotype, mild and transitive, may therefore have clinical significance. However, we should remember that the commencement of treatment is available only for people with active form of disease, and the percentage of plasma cells in the bone marrow does not affect the decision about treatment. In the smoldering form of PCM risk of disease progression can be assessed by testing the free light chains in serum (SFLC, serum free ligt chains). The ratio of kappa/lambda above 8:1 or less than 1:8 is associated with more rapid progression to full-blown form of PCM (Jamroziak et al., 2013).

The pathogenesis of multiple myeloma is still unclear, but possible causes include exposure to pesticides, radiation, insecticides, organic solvents, dyes and hair coloring products, and other occupational and environmental factors (Beason et al., 2012).

Chromosomal additions, deletions, translocations, are associated with the risk of the disease and almost all of these aberrations are associated with the occurrence of MGUS.

There are two forms of the disease. Hyperdiploidal form, comprising 47–74 chromosomes, resulting mainly in the presence of trisomy of chromosomes odd-numbered 3, 5, 7, 9, 11, 15, 19 and 21, and a small number of translocations. The second non-hyperdiploidal embodiment is characterized by abberations of a hypodiploid with chromosome number ≤44, pseudopodium with chromosome number 45 or 46, and tetrapoidal form in which the number of chromosome is ≥75. These forms are characterized by a large number of coexisting region translocations of heavy chain immunoglobulin genes IgH (locus *14q32.33*) to various proto-oncogenes, among which the most common are located at the locus of the gene CCND1 encoding the D1 cyclin, CCND3 locus encoding the D3 cyclin, gene locus FGFR3 and MMSET, gene locus CMAF and gene MMFB. Summary information on

the gene expression of cyclin D with cytogenetic state of *14q* translocation allowed for the preparation of molecular classification of multiple myeloma, called the TC (Translocation/Cyclin) classification. The division into classes with different molecular classes, multiple myeloma with different prognosis is determined for the cyclin D expression, coupled with an appropriate translocation of IgH or lack of it. *14q* IgH translocation is one of the most frequent chromosomal abnormalities in MM. About 60% of the translocation involves the repeating 5 aberrations: *11q13*, *4p16*, *16q23*, *20q11*, *6p21*, which affect the expression of the corresponding genes, including cyclin D1-D3. Gene overexpression of cyclin D1 and D3 (connected with proper *14q* translocation) has a better prognosis than the over-expression of cyclin D2, coupled to a different *14q* translocation. TC classification, despite the undeniable prognostic value, is not frequently used in clinical practice due to both the low availability and high cost of research. The progression of multiple myeloma is associated with secondary cytogenetic changes, which were mentioned above, and various deletions, among which the most important is a deletion in the range of chromosome 17, leading to the heterozygosity of the p53 gene, which is associated with resistance to treatment. Suppressor gene p53 is considered a very important prognostic factor in multiple myeloma, it is an indicator/marker for predicting transition sharpened disease state. Moreover, deletion of *17p13* is associated with relapse in a short time even after administration of high-dose chemotherapy and shorter survival times after transplantation of allogeneic stem cells. 17 chromosome aberrations: t (4; 14) and t (14; 16) are detected in 85–90% of patients and are associated with a deletion of chromosome *13q14* (Walewski, 2011; Nadiminti et al., 2013; Dmoszyńska, 2015).

## Symptoms

Symptoms of multiple myeloma can be in the early stages of the disease confused with a common cold. We can note fever, lack of appetite, weight loss, night sweats and recurring colds. Local propagation of malignant plasma cells in the bone marrow may cause primarily painful osteolytic lesions, as well as anemia, kidney failure, and elevated levels of calcium. Impaired plasma cells release cytokines that stimulate the degradation of bone. These include: interleukin-1b (IL-1), tumor necrosis factor (TNF) – A, B-TNF, interleukin-6 (IL-6), macrophage colony stimulating factor (M-CSF), vascular endothelial growth factor (VEGF), and other cellular growth hormones. All of these cytokines are activators of osteoclasts (OCs) (Dmoszyńska, 2011; Ludwig et al., 2011; Molassiotis et al., 2011; Jamroziak, Warzocha, 2015).

Organ dysfunction subsidiary of PCM described as CRAB (calcium increased, renal insuficiency, anemia, bone lesions) (Jamroziak et al., 2013) – see Table 1.

**Tab. 1.** Organ symptoms criteria being the base for diagnosis of symptomatic multiple myeloma (CRAB symptoms) (Jamroziak, 2013)

| | |
|---|---|
| C<br>Hypercalcemia | Corrected calcium >0,25 mmol/l above the upper limit of the reference value or >2,75 mmol/l |
| R<br>Renal insufficiency | Creatinine concentration in serum >173 umol/l (2 mg/dl) |
| A<br>Anemia | Hemoglobin concentration of 2 g/dl below the lower reference value or < 10 g/dl |
| B<br>Bone lesions | Lytic lesions or osteoporosis with compression fractures |
| Other | Recurrent bacterial infections (>2 in the last 12 months), hyperviscosity syndrome, amyloidosis |

Three-digit ESR, osteoporotic changes in spine, the presence of monoclonal protein in Electrophoresis – are the changes that may indicate multiple myeloma. Osteolytic lesions occur in 66% of patients. More than half of the patients reported pain (58%), which guide the patient more frequently to a rheumatologist or orthopedist than hematologist. Bone osteolysis contributes to the occurrence of hypercalcemia, which can manifest itself clinically by: nausea, vomiting, polyuria, hypercalciuria, headaches, and even disturbances of consciousness (Heher et al., 2013).

## Modern methods of multiple myeloma diagnosis

Thanks to the development of modern diagnostic techniques it is possible to determine illness changes earlier and more accurate. In the case of plasmacytoma diseases, most commonly used is the magnetic resonance imaging (MRI), and histopathological examination of biopsy tissue, cytogenetic studies or FISH, positron emission tomography (PET), and polyclonal determination of free light chains in serum (FLC, FREELITE).

MRI is a non-invasive imaging method, especially useful for the detection of tissue lesions. This test most commonly determines the level of changes in the spine and other bone tissues. Histopathological examination is a microscopic examination of the cytological material (cell) or histological one (tissue). In this study, we can distinguish two stages. The first stage is to acquire the material by various methods, among others, with biopsy. The second step is the evaluation by laboratory techniques. Fine needle aspiration biopsy (BAC, puncture) BAC is called the method of collection of cellular material (cytology) through a tumor puncture done with a thin needle. Thanks to the reduced communication, which is characteristic by its thread tissue for most cancers, easily aspirated (sucked) into the needle, cells of solid tumors expanding in the depths of tissue. Fine needle biopsy is used to determine the diagnosis of palpable and impalpable tumors.

Cytogenetic studies include evaluation of chromosomes obtained from the cell core. The research aims to determine the karyotype of cells: the number and structure (morphology) of chromosomes in metaphase stage of mitotic cell cycle, or

cytogenetic karyotyping. The test is performed in order to detect karyotype irregularities: quantitative chromosome aberrations: disorders of the amount of genetic material in the cell – aneuploidy, or structural aberrations (changes in the distribution of materials in the chromosome) – such as inversions, deletions, translocations.

FISH (eng. fluorescent in situ hybridization) is a cytogenetic technique to determine the sequence of DNA using fluorescence microscopy. FISH technique allows the quantitative analysis using fluorescence scanning confocal microscope (eng. confocal laser scanning microscope, CLSM).

PET (eng. position emission tomography) is a three-dimensional imaging technique which register changes during positron annihilation. These studies allow an early assessment of metabolic changes in the tissues of patients. The contrast of glucose combined with a fluorine isotope (18F). It is a marker extensively metabolized by cancer cells.

FLC (eng. serum free light chains analysis) is a polyclonal determination of free light chains in serum. This method uses two immunodiagnostic tests using polyclonal antibodies which allow to quantitatively evaluate: free kappa chains (κ) in serum, free lambda chains (λ) levels, and the ratio of one to the other. The test is particularly effective for nonsecretory myeloma (Jamroziak, 2015).

## The most common complications

Hypercalcemia is a common metabolic complication of multiple myeloma. This is mainly caused by bone resorption caused by tumor. In patients with impaired renal function, hypercalcemia may be aggravated by decreased excretion of calcium.

Hypercalcemia diagnosis based only on increased levels of calcium in serum is unreliable as the tendency for the binding of albumin circulating calcium can lead to a deficiency of a biologically active calcium. The success of treating MM is prevention related to the treatment of symptomatic hypercalcemia. Appropriate treatment should begin with the intravenous administration of physiological saline, forced diuresis salt, and monitoring of central venous pressure and serum electrolytes. Steroids, which are normally administered to patients, not only have anti-inflammatory action, but also hinder the absorption of calcium and reduced bone mineral density (Ailawadhi et al., 2010).

Another dangerous complication of multiple myeloma is renal insufficiency, and is associated with increased mortality in patients with MM. Different pathogenic mechanisms, some of which result from the action of neurotoxic monoclonal Ig proteins, are independent of protein M deposition. Included as monoclonal gammopathy kidney damage are cylinder nephropathy, glomerulopathies, amyloidosis, hypercalcemic nephropathy, acute and chronic interstitial nephritis, acute gouty nephropathy, nephropathy, hyperviscosity syndrome, direct infiltration of the kidney (Shay at al., 2016; Surowiec et al., 2016).

Diagnostic standard is protein electrophoresis, inexpensive test, which unfortunately has poor sensitivity for the detection of free light chains, and cannot always distinguish between the expansion of the polyclonal or monoclonal light chains of the protein. Test FLC has a much higher sensitivity than electrophoresis, but this is a qualitative test and thus has limited usefulness in monitoring the MM and response to treatment. A novel assay allows the quantitative statement of free light chains in serum, and promotes early diagnosis, and allows for early detection of relapse. New methods of diagnosis of myeloma showed significant progress in reversing the renal failure in some cases and improvement of results (Shay et al., 2016).

Anemia affects about 60%–70% of patients with myeloma. Because of the delayed diagnosis, it may pose even life-threatening danger. The most common is normocytic anemia (deficit of normal red blood cells in the blood). The parameters usually improve with the response to treatment. The use of erythropoiesis--stimulating agents (ESA) on patients should be considered when, despite response to chemotherapy, there was no increase of hemoglobin. During treatment there should be monitored the amount of iron in the blood, prevent the loss of functional iron to support erythropoiesis. Transferrin saturation should be at least 20% and ferritin concentration at least 100 ng/ml (Ailawadhi et al., 2010; Gay, Palumbo, 2010; Jamroziak, 2013).

Clinically, the most characteristic disorder in MM is bone pain caused by osteolytic changes. The number and activity of osteoclasts (OCs) increase in the accumulation of myeloma cells. Produced by stromal cells of the bone marrow/osteoblasts RANKL (receptor activator of nuclear factor-kB ligand), the main molecule in the regulation of normal osteoclastogenesis in response to its receptor RANK (receptor activator of nuclear factor-kB), it stimulates osteoclastogenesison on OCs precursors, whereas OPG (osteoprotegerin) secreted by the stromal cells/osteoblasts bounds RANKL and prevents the interaction of RANKL and inhibits osteoclastogenesis (Zdzisińska, Kandefer-Szerszeń, 2006; Shay et al., 2016). In normal bone tissue homeostasis between RANKL and OPG protein is exactly balanced. In myeloma balance between OPG and RANKL is imbalanced, frequently observed is abnormal production of OPG (Ludwig et al., 2011).

Myeloma cells enhance local osteolysis by increasing the expression of RANKL and reduction in the expression of OPG in the bone marrow, and as a result degradation of OPG bound by tumor cells through Syndecan-1. An additional factor affecting the imbalance of RANKL/OPG and enhancing osteolysis, may include a direct production of RANKL by myeloma cells. Activation of OCs is accompanied by the simultaneous inhibition of osteoblasts osteogenic activity, which are the result of a direct reaction of this cells with myeloma cells, and the inhibitory effect of various elements emitted by the myeloma cells. Restoring the balance between RANKL and OPG not only slows down the resorption of bone induced by the disease, but suppresses growth and survival of myeloma cells (Jamroziak, Warzocha, 2015).

After diagnosing the symptoms of the disease, it is important to start appropriate treatment. Pretreatment often consists of high-dose chemotherapy and bone marrow or bone marrow stem cells transplant. A bone marrow transplant should not be performed at the beginning of treatment, it is better to introduce it at a later date. Adjunctive therapy alleviates the physical and emotional impact of the disease on the patient's life. In this case are used: blood transfusion, analgesics and antibiotics. Patient should also keep adequate physical activity, diet and regular sleep.

Until recently, myeloma was considered a deadly disease. Thanks to modern diagnostic techniques and modern medicine it has become a chronic disease.

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### Abstract

Cancer is a state in which your cells divide in an uncontrolled way and acquire different characteristics from typical cells of the affected organ. The uncontrolled cell division is caused by protein coding genes mutation, which participate in cell cycle. A malignant tumour is connected with multiple mutation and this is why the disease duration is long and asymptomatic. Unfortunately, most cases of cancer are diagnosed when the tumour is already identifiable or when the patient shows other disturbing symptoms (Jędrzejak, 2009).

Tumours which stem from bone marrow plasmatic cells belong to a group of rare diseases which involve, among others, plasma cell myeloma (PCM), plasmocytoma, maternally inherited diabetes and deafness (MIDD), and monoclonal gammapathy of undetermined significance (MGUS) (Jamroziak, 2013).

Multiple myeloma (MM) originates from the aforementioned plasma cells which are responsible for the production and secretion of antibodies, as well as humoral immune response. MM is caused by clonal proliferation plasma cells which displace healthy cells and cause gradual bone destruction (osteolysis). Additionally, plasma cells produce pathological monoclonal protein (present in blood or urine), which usually involves class IgG and IgA immunoglobulines. Sometimes, monoclonal protein is not a whole immunoglobulin particle, but only its free light chains.

The illness develops in bone marrow, mainly in the backbone, the ribs and the skull. The name multiple myeloma comes from the fact, that it is a metastatic cancer. MM is not a well known disease, and only 1 out of 50 respondents recognized it.

**Key words:** multiple myeloma, etiology of multiple myeloma, epidemiology, prognostic factors, genetic mutations, chromosomal abberration

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