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„Българска медицина“ се реферира в международната база данни Index Copernicus International
Affectives disorders, stress and neuro-inflammation

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Abstract

Neuro-inflammation represents the immune-related processes in the central nervous system (CNS), acute, appearing after psychological stress, trauma, infections or neurological pathologies, and chronic, associated with neurodegenerative disease and possible cognitive degradation. The inflammatory process is also directly linked with CNS and cardiovascular disease, being predicted by the levels of high sensitivity C protein. Cellular biological and biochemical mechanisms of inflammatory processes are very complex, our paper aimed to gather the latest and the most relevant proofs that link the psychiatric, and especially affective disorders, stress and neuro-inflammation.

Keywords: inflammatory process, high sensitivity C protein, immune system, stress, depressive disorder

Introduction

In general, the term neuro-inflammation is used to describe the immune-related processes that took place in the central nervous system (CNS). The acute neuro-inflammation process that takes place in the CNS are usually in a context dependent situation and can appear after psychological stress, trauma, infections or neurological pathologies. The transient inflammatory response is in general beneficial for the CNS. However the chronic inflammation exposure is associated with neurodegenerative disease and possible cognitive degradation. (57, 58). The researcher’s understood the neuro-inflammation models by observing the traumatic CNS injuries and infections (25, 63) or experimental model of the neurological diseases in pathological or non-pathological conditions (65). For example, the transient increase of the cytokines production will induce adaptive and beneficial behavioral and physiological response that will help the body to fight the pathogens (18, 19). Also, an example of non-pathological neuro-inflammation (a condition that do not exhibit loss of CNS integrity, significant breakdown of the brain-blood barrier (BBB) or infiltration of the CNS by peripherals immune cells (57, 58, 6, 7).

We also have to take into account that in the classic medical literature, the SNC is described as an immune privileged organ, that do not have the adaptive arm of the immune system (for example: B cell or T cells), and has a diminished cellular immune function but lymphocytes still provides the immune surveillance (31, 28). The T cells are present in the cerebrospinal fluid, meninges and choroid plexus (48) and for example, in the MS patients that received treatment that blocks these cells to enter the CNS, the incidence of CNS virus encephalitis increases (96, 46, 95). The cells that comprise the BBB have also the role to facilitate the neuro-immune communication (58).

For example the astrocyte (that compose the glia limitans) that has as origins some neural progenitors, when is activated it increases the IL-1β, CCL2, PGE2, TNFα, the reactive oxygen species (ROS) and modulates the glutamate level (they can indirectly increase it or take the excess of glutamate from the synapse level and converts it to glu-
When it is activated, microglia from CNS acts similar to activated macrophages from the periphery, by upregulating the antigen presentation molecules (MHC-II) and other pathogen recognition receptors (TLRs) (20). Moreover, on activation the microglia becomes de-ramified with a retracted process and the cell body becomes hypertrophic exhibiting macrophage like function: phagocytosis, proliferation, cytokine production (inflammatory cytokines: IL-1β, IL-6, TNF-α and anti-inflammatory cytokines: TGFβ, IL-10) that increases the production of chemokines and secondary messengers (prostaglandins, neurotransmitters, nitric oxide) (33, 80, 50, 47). This interactions between inflammation and CNS are very important when they are related to stress and depression because the animal model experiments (on rodents for example) have showed that primed microglia on aged rats respond to inflammatory stimuli with prolonged neuro-inflammation that leads to behavioral consequences like depressive-like behavior and social withdrawal (99, 36, 49, 17). Aberrant neuro-inflammation and microglia dysregulations are associated also with anxiety, schizophrenia or obsessive compulsive behavior (5, 14). The IL-1 binding to IL-1 receptors activates mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) pathways that initiate the inflammatory cascade (72, 54). Moreover cytokines activation promote the production of secondary messaging and other cytokines (for example circulating IL1 stimulates perivascular macrophages to produce PGE2 that activates brain stem nuclei that in turn mediate the HPA axis response) (27). On the other hand, the anti-inflammatory cytokines like TGFβ, IL-10 and IL-1Ra can directly reduce the transcription and translation processes of the inflammatory cytokines by inhibiting the NF-κB and MAPK signaling (94).

The CNS macrophages are derived from monocytes that resides in the perivascular space, choroid plexus and meninges. Their role is similar but more intense that the role of the astrocytes. For example, in response to the peripheral inflammatory cytokines, the CNS macrophages produces prostaglandins like PGE2 that regulate the hypothalamic-pituitary-adrenal axis function (HPA axis) and also regulates the febrile response (87). The intensity and the duration of the inflammatory stimuli can influence the perivascular macrophages to inhibit the endothelial cells in order to reduce the prostaglandin signaling in the CNS parenchyma. In the opposite, the depletion of the CNS macrophages causes exaggerated PGE2 synthesis by endothelial cells that leads to a HPA axis response and protracted febrile syndrome (88).
Regarding the phagocytosis function and antigen presentation function of the macrophages in the CNS, the studies showed that there is a limited proportion of the dendritic cells but with the ageing process that percentages increases (11, 29, 51). In particular, the neuro-inflammation process is associated with an increased expression of the inducible nitric oxide synthase (iNOS) that generates the nitric oxide (NO) (84). The NO can act as a neuromodulator but during the neuro-inflammation process it has such high levels that it can cause cellular damage (71). In addition, another function of the cytokine signaling is to promote recruitment of peripheral immune cells to the sites of inflammation by binding on the specific chemokines receptors (CCR2) (for example IL-1β or TNF-α can facilitate this process the infiltration of the CNS by peripheral immune cells) (12). In practice this is important because in models of Alzheimer disease, the CCL2 production at inflammatory loci near amyloid plaques recruits CCR2+ monocytes to help clear the amyloid depositions (26). In particular, recent evidences suggest that CCL2 and CX3CL1 mediate the recruitment of monocytes in CNS but the expression of CCR2 is specific for the monocytes subset with an increased inflammatory potential and the high expression of CX3CR1 is indicative of resident, homeostatic monocytes (69). The inflammatory cytokines also have the role of activating the kynurenine 3-monooxigenase (KMO) and indolamine 2,3-dioxygenase (IDO) that is responsible for breaking down tryptophan (a precursor of serotonin) into kynurenine and this is why the increase IDO activation during neuro-inflammation reduces tryptophan availability and decreased serotonin levels (69). On top of that, kynurenine can be converted by KMO into 3-hydroxy-kynurenine and after into quinolinic acid that can initiate glutamatergic exo-toxicity and promote degeneration of susceptible dopaminergic neurons (93).

In conclusion, the communication of the CNS with the immune system is a 2-way street and chronic or extended neuro-inflammation can directly influence even the serotonergic, dopaminergic and glutamatergic neurotransmission or even the CNS structure (66). This interaction is not always a bad thing because, for example social redrew and antisocial like behavior during an acute infection can be a way to naturally limit the infection spread but can decreased the host survival chances (61, 54).

Objectives and methods

The main objective of this article is to gather the latest and the most relevant proofs that link the psychiatric disorders and especially the major depressive episode (MDD) and neuro-inflammation.

Results

Generally, the stress is defined as being a complex response (behavioral, psychological or biological) to an aggressive or instigating stimuli that overpass the body or/and mind available resources to cope with this demands (35, 22). The main discussion in this case is nature of the stressor because it has been proven that acute phase stressors (brief and predictable) may have a beneficial effect in term of enhancing cognition emotion and immune and neurobiological systems (22, 23).

It is now, generally accepted that the biological stress concept is linked to the HPA axis activation, renin-angiotensin-aldosterone (RAA) system and autonomic nervous system, that all bidirectional communicate with the immune system. So, practically the response to stress involves modification of the: hearth rate, blood oxygen saturation, down-regulation of the neurobiological system that reduces reproduction, digestive growth and of course tissue breakdown (15, 37).

As a response to a stressor, the body releases pituitary adrenocorticotropic hormone (ACTH) because the corticotrophin release factor (CRF) was secreted by the parvocellular neurons from the hypothalamic paraventricular nucleus (PVN). The sympathetic nervous system and ACTH signal to the adrenal glands to secrete catecholamine and cortisol. In this context, the adrenal glucocorticoids (CGS) will modulate the HPA axis activity by giving a feedback to the hypothalamus, pituitary and hippocampus (37, 85). But there are many extra hypothalamic CRF projections that are regulating that feedback system (but not very well documented in the literature). So the autonomic nervous system interacts with the HPA axis and the RAA system, by these pathways. Moreover, the CRF activates the locus coeruleus and by that increases adrenals and noradrenaline secretion of catechol amines that increases the hearth rate and the blood pressure by sympathetic activation and parasympathetic inactivation (10, 30).

The CNS can also mediate or starts an inflammatory reaction, because the nerves that are containing inflammatory peptides can participate in an inflammatory reaction caused by stress, trauma or infection (32) and this is called neurogenic inflammation. The response of the stimulation of the CNS by the stimuli (chemical, electrical, mechanical, heat) includes the arteriole vasodilatation, plasma extravasation from the post-capillary venules because the nerves releases neuropeptides like substance P (6). Interestingly, local anesthetic use or nerve damage will not generate such
a response because the peripheral nervous system must be intact in order to respond (6).

The relationship between acute and chronic stress in inflammatory disease like cardiovascular disease is based on the activation of the sympathetic nervous system, the hypothalamic-pituitary axis, and the renin-angiotensin system, causes the release of various stress hormones such as catecholamine, corticosteroids, glucagon, growth hormone, renin and elevated levels of homocysteine, which induce a heightened state of cardiovascular activity, injured endothelium, and induction of adhesion molecules on endothelial cells to which recruited inflammatory cells adhere and translocate to the arterial wall (7). The acute is characterize by the macrophage activation, the production of cytokines, other inflammatory mediators, acute phase proteins (APPs), and mast cell activation, all of which promote the inflammatory process (7). Stress also induces an atherosclerotic lipid profile with oxidation of lipids and, if chronic, a hypercoagulable state that may result in arterial thromboses (7). Shedding of adhesion molecules and the appearance of cytokines, and APPs in the blood are early indicators of a stress-induced acute phase response that may appear in the blood of asymptomatic people, and be predictors of future cardiovascular disease (7). The inflammatory response is contained within the stress response, which evolved later and is adaptive in that an animal may be better able to react to an organism introduced during combat (7). The argument is made that humans reacting to stressors, which are not life-threatening but are "perceived" as such, mount similar stress/inflammatory responses in the arteries, and which, if repetitive or chronic, may culminate in atherosclerosis (7).

In neuro-inflammation and in the relationship between stress and cardiovascular disease the substance P (SP) plays a crucial role (6). It is widely present in the CNS and in the peripheral areas (in autonomic afferents fibers and in unmelylated sensory fibers) and it is an 11-amino-acid bioactive peptide with a central role of mediates (as neurotransmitter/neuromodulator) the stress response by binding with the neurokinin-1 receptor in special areas like the prefrontal cortex and amygdala (82). Additionally, the SP activates HPA axis that results in CRF and ACTH increase, during psychological stress. Moreover, many immune cells have SP receptors that once activates trigger the inflammatory cascade (6). The psychological stress like the one produced by social redraw releases SP from the sensory nerve fibers and the SP modulates the mast cell degranulation that result in the release if several inflammatory mediators (89).

Another stress hormone is considered to the Y neuropeptide (NPY) secreted by the postganglionic sympathetic nervous system that is a non-adrenergic co-mediator of the catecholamine’s actions (58). It has been found to have an anxiolytic effect on animal models of anxiety and the human studies suggest that post-stress levels of NPY are negatively correlated with psychological distress suggesting that the NPY may buffer against the psychological stress (64). Besides anxiety, the NPY also have a role in feeding, energy balance, and atherosclerosis and of course on inflammation because the T, B and NK cells also have specific NPY receptors (58, 64, 45).

The catecholamine (epinephrine - E, nor-epinephrine - NE and dopamine - DA) are released as response to stress and their main purpose is to prepare the body for the flee/fight mechanism but the NE, which is secreted by adrenal medulla but also from the sympathetic fibers, have an effect on the immune system (42). They have both pro and anti-inflammatory properties, especially NE by stimulating the cytokine release from macrophages (β and α receptors) (32).

If the typical catecholamine (cortisol, corticosterone) response can be measured in the first hours from the stress, the effects of the glucocorticoids (GC) secreted by the adrenal cortex, can be measured on long term. Their secretion and synthesis is regulated by ACTH and their action is due to their effect on two types of receptors (mineralocorticoid-MR and glucocorticoid receptors-GR) (21). It was discovered that the MR have a much higher affinity for GC and this is why, at basal level the GC are bond mainly to the MRs (93). In consequences, only on moderate to severe stress levels the GRs became occupied, after all the MRs are fully occupied (91). But their distribution is not equal through all the body, for example in the CNS the GRs are much more expressed (32) and by this two data combine we can fully understand their different effect depending on the stress level. Centrally they offer a feedback signal to modulate the HPA axis activity, mobilize the body energy to the muscle (by regulating the glucose uptake), and reduce the immune system activity and actively suppress inflammation (91). In the periphery the CG effect is variable depending from the type of stress: the acute stress seems to increase the immune system activity and the chronic stressor effects are suppressive (86, 92).

The cytokines are the largest soluble proteins and their primary function is to the local and systemic inflammatory response to pathogens or other type of aggression (16). They are classically divided into four groups: the pro-inflammatory cytokines that are playing a major role in the non-specific immunity, like IL-1β, IL-6 or TNFα; the cytokines that help to induce cytotoxic immunity (1st type T helper); the 2nd type T helper that have an anti-
inflammatory role and 3rd type T helper that are immunosuppressive (16). It is has been said that the imbalance between pro and anti-inflammatory cytokines can lead to psychological and physiological disorders (53).

In maintaining this balance the nuclear transcription factor (NFκB) that is highly expressed through CNS also plays an important role (67). It is activated (as stimuli by infections, cytokines, UV light, etc.) by a sequence of enzyme complexes and after activation enters in the cell nucleus where it binds to the specific DNA sequences in the promoter region of the targeted genes. These genes code among others, the code for protein involvement in the oxidative stress (67). The NFκB also explains the CG dual role as pro and anti-inflammation because if the activated CG receptors have the affinity also for NFκB (preventing it to migrate to nucleus) but also mediate increases of LPS-induced NFκB in the frontal lobe and hippocampus after the exposure to chronic stress (68).

In the neuro-inflammation process another key player is the nitric oxide (NO). The NO is a diffusible gas and its effects are not restricted to the site of production (microglia, macrophage, NK cells, dendritic cells, phagocytes, smooth muscle cells, epithelial cells, neutrophils and neurons) and travel free or linked great distances in the body (8). It reacts directly with cells, proteins, non-organic molecules and DNA (8). The NO is generally produced at the cells level by the Nitric Oxide Synthase (NOS). The NOS has tree forms: neuronal, endothelial and inducible (expressed during inflammation processes (39). iNOS mediates the cytotoxicity caused by oxidative stress, prolong NO release and the production of others oxidant species like oxynitrate that can damage proteins, DNA and mitochondria, in the same time being able also to participate to the upregulation of the pro-inflammatory signal transduction path (39). This way the vicious circle of inflammatory damage happens: the cytokines induce high expression of the iNOS that produce NO, oxynitrate and upregulate the pro-inflammatory signal that increases cytokines production (39). Chronic stress produces a high level of iNOS that can contribute to CNS disease including Alzheimer’s disease (AD), Parkinson disease (PD), stroke, or multiple sclerosis (59).

The cyclooxygenase (COX) have three different forms (COX 1- present in all the tissues, COX 2- present in the brain and in other few tissues and COX 3 that is variant of COX2) is responsible for the secretion of prostanoids involved in the pathological inflammatory affections and peroxides or prostaglandin E2 in toxic doses (32). This products can cause tissue damage by generation free radicals (NO) and by inducing apoptosis by the induction of the glutamate release from the astrocytes (32). Studies showed that stress increases the COX 2 mRNA levels (60), so there is an additional inflammatory pathway in the communication between CNS and the immune system.

**Discussions**

The inflammatory process has been proven to be crucial both for CNS and cardiovascular disease. One of the most frequent inflammatory biomarker for the prediction of cardiovascular death or morbidity is the high sensitivity C protein (hs-CRP) (75).

CRP is an acute-phase reactant synthesized by the liver in response to cytokines released by damaged tissue. Production is controlled by interleukin-6, an inflammatory cytokine (97). CRP is commonly measured to screen for inflammation or infection and CRP is produced by cells in the vascular wall such as endothelial cells, smooth muscle cells, but also by adipose tissue (97).

Chronic inflammation is pivotal in heart disease; studies have shown that high levels of CRP, measured by high-sensitivity CRP (hs-CRP), can be a marker of atherosclerosis. hs-CRP is an important predictor for cardiovascular events including myocardial infarction, cerebrovascular events, peripheral vascular disease, and sudden cardiac death in individuals without a history of heart disease (13). In patients with acute coronary disease, CRP level predicts mortality and cardiac complications. High CRP levels portend a worse prognosis in patients with acute coronary syndromes and also hs-CRP is also a marker of metabolic syndrome (13).

The relative risk of future cardiovascular events based on hs-CRP testing is estimated as follows (75):

- Low risk: hs-CRP < 1.0 mg/L;
- Intermediate risk: hs-CRP 1.0-3.0 mg/L;
- High risk: hs-CRP > 3.0 mg/L;
- Acute inflammation is a CRP greater than 10.0 mg/L.

Relative risk in the high-risk group is estimated to be twice that in the low-risk group (75). The specific recommendations on the use of hs-CRP testing in the assessment of cardiovascular risk in asymptomatic adults, from the American College of Cardiology Foundation and the American Heart Association includes (38):

- hs-CRP testing may be useful in selecting patients for statin therapy in men 50 years and older or women 60 years and older with LDL less than 130 mg/dL who are not on lipid-lowering, hormone replacement, or immunosuppressant therapy, who are without clinical CHD, diabetes, chronic kidney disease, severe inflammatory conditions, or contraindications to statins (38);
- hs-CRP testing may be reasonable for cardiovas-
cular risk assessment in asymptomatic men 50 years and older or women 60 years and older at intermediate risk (eg, based on Framingham Risk Score) (38).

- hs-CRP testing has not been shown to be beneficial for cardiovascular risk assessment and is not recommended in asymptomatic high-risk individuals (38).

The hs-CRP also predicts the improvement of the depressive symptoms in patients with type 1 diabetes and depression (101). Depression score was also correlated to hs-CRP levels in women (100). Further studies are required to elucidate the biological mechanisms underlying these associations and their implications, but also to confirm this cheap and easy to make inflammatory parameter as a screening tools for depression or CNS inflammation.

Conclusions

Many studies showed that the brain and the immune system communicate bidirectionally and the stress can have a direct impact on CNS and on the immune functions in the same time. It can induce and modulate inflammatory processes that alter the CNS pathways. Also stress can cause anxiety, social redrew or depression and on long term PD, AD, stroke or multiple sclerosis.

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Overweight and high level of nicotinamide phosphoribosyltransferase as factors contributing to osteoarthritis progression and metabolic syndrome development

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Abstract

Aim
To study the effect of weight loss over 5 kg on the clinical manifestations of OA, indicators of water, lipid metabolism and visfatin serum levels in patients with OA.

Materials and methods
We studied dynamics of clinical symptoms, markers of carbohydrate, fat metabolism and visfatin level before and after weight loss in 80 patients with osteoarthritis. Nicotinamide phosphoribosyltransferase (visfatin, Nampt) level in serum was determined by indirect solid phase ELISA using a test systems (RaiBiotech, cat № EIA - VIS -1).

Results
As a result of our study patients with OA with weight loss of more than 5 kg had more obvious pain relief than patients with the original weight. At the same time a significant improvement has been seen in carbohydrate and lipid metabolism. These findings suggest that there is a possible role of visfatin in the pathogenesis of osteoarthritis.

Conclusions
All patients with OA with a BMI over 25 kg / m 2 are recommended to lower their weight to decrease the mechanical stress on the joints, and also to reduce the severity of inflammation and metabolic disorders.

Keywords: visfatin, nicotinamide phosphoribosyltransferase, Nampt, osteoarthritis, overweight, metabolic syndrome.

Osteoarthritis (OA) - the most common joint disease. The risk factors of OA are considered to be genetic predisposition, overweight, professional, sport and everyday overloads, injuries, age over 50 years and other joint diseases [11, 16]. Studies in other countries found that the prevalence of back and neck pain is associated with increased BMI. According to the authors of these studies there is a relationship between the chemical and metabolic mechanisms of OA and overweight. The relation between obesity and OA of the hand joints suggests the presence of other pathological mechanisms except for the load weight on the cartilage [1, 4, 9, 12].

Obesity is a condition that prolongs chronic inflammation and promotes synthesis and secretion of pro-inflammatory factors by adipose tissue, such as classical cytokines (interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor-□ (TNF-□)), adipokines (leptin, adiponectin, resistin) [8, 9] and other newly identified proinflammatory factors (hemenin, lipokain, serum amyloid protein 3) [5]. The adipose tissue contains many stromal fibroblasts, which secrete adipokines. With an increased amount of adipose tissue the number of macrophages infiltrating it also increases. These data is based on the hypothesis that inflammation in adipose tissue may be the reason for systemic and metabolic disorders [7].

Nowadays one of the most actively studied adipokines is nicotinamide phosphoribosyltransferase (visfatin, Nampt). Many studies have shown that its level increases in obesity [6, 8]. Visfatin is directly involved in the pathogenesis of vascular inflammation - the main cause of atherosclerosis [10], it can also affect the inflammation in local tissues and together with other adipokines influences the development of OA [11, 15].

It is proved that obesity is associated with the
progression of OA, with the presence of hypertension, dyslipidemia, and to a lesser extent with diabetes and glucose resistance [4, 14]. Probably these conditions have common pathogenic mechanisms. The results of the previous studies have shown that weight loss leads not only to decreased clinical activity of osteoarthritis, but also results in lowering of proinflammatory cytokines and adipokines (leptin, resistin, IL-6, soluble receptor TNF-α et al.) [2, 5, 13], we can assume that weight loss in patients with OA will not only result in clinical improvement, but also will reduce visfatin concentration in blood serum, as well as decrease the severity of metabolic changes.

**Objective:** To study the effect of weight loss over 5 kg on the clinical manifestations of OA, indicators of water, lipid metabolism and visfatin serum levels in patients with OA.

**Materials and methods.** We observed 110 people: 80 patients with OA and 30 healthy individuals in the control group. All patients provided written informed consent to participate in the study according to the Helsinki Declaration. According to the dependence of visfatin level on body mass index (BMI), people with BMI of 25 to 30 kg/m², aged 18 to 79 years participated in the study, in the presence of OA evaluated with the criteria of the American college of Rheumatology (1986, 1991), the Institute of Rheumatology RAMS (1993 г.) [16], and diagnostic criteria by Althman R. D. (1991, 1995 гг.) [3].

Patients with different forms of OA ranged in age from 36 to 78 years, of whom there were 52 (65%) women (mean age 52.08 ± 1.58 years), and 28 (35%) of men (mean age - 54.07 ± 2.0 years). Patients with OA were comparable in age with the control group (t = 1.97, p > 0.05 and t = 2.0, p > 0.05, respectively). The control group consisted of 20 women and 10 men aged 22 to 55 years with no complaints of pain in the joints over a lifetime, and without clinical signs of OA.

Visfatin level in serum was determined by indirect solid phase ELISA using a commercial test systems (RaiBiotech, cat № EIA - VIS -1), level of C-reactive protein (CRP) in the blood serum was determined by ELISA - “Hema-Medica” (St. Petersburg). Glucose, triglycerides, HDL and LDL levels were determined by standard techniques before treatment and 3 months after that. Baseline characteristics were not significantly different.

**Results.** As overweight patients were recruited in the study, hypocaloric diet low in animal fats and physiotherapy has been recommended to all participants. The positive dynamics in body weight loss over 5 kg within 3 months has been achieved by 18 patients (23%). Only nonsteroidal antiinflammatory drugs in standard dosages were prescribed as a drug therapy for all patients with OA. All patients were divided into two groups to study the effect of weight loss on the clinical manifestations of OA. The first group consisted of patients who were able to reduce body weight by 5 kg and more (18 pers.), the second group - patients with weight reduction of less than 5 kg and patients without any weight loss (62 pers.). Carbohydrate and lipid metabolism as well as visfatin concentration were evaluated in these patients groups, received data represented in the table below (Table 1).

**Table 1.** Visfatin level, instrumental and laboratory data in patients with OA due to body weight loss

<table>
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<th>Group 1</th>
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<th>The reliability of differences between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 18</td>
<td>n = 62</td>
<td></td>
</tr>
<tr>
<td>Visfatin level (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>4.33 ± 0.39</td>
<td>3.84 ± 0.24</td>
<td>t = 5.81, p = 0.001</td>
</tr>
<tr>
<td>After treatment</td>
<td>2.46 ± 0.25</td>
<td>3.35 ± 0.30</td>
<td></td>
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<tr>
<td>Dynamics</td>
<td>1.93 ± 0.24*</td>
<td>0.45 ± 0.08*</td>
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<tr>
<td>CRP level (mg/L)</td>
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<tr>
<td>Before treatment</td>
<td>9.23 ± 1.30</td>
<td>9.38 ± 0.38</td>
<td>t = 3.99, p = 0.001</td>
</tr>
<tr>
<td>After treatment</td>
<td>6.01 ± 0.74*</td>
<td>4.94 ± 0.12</td>
<td></td>
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<tr>
<td>Dynamics</td>
<td>5.70 ± 0.62*</td>
<td>0.46 ± 0.11</td>
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<td>Fasting glucose level (mmol/L)</td>
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<tr>
<td>Before treatment</td>
<td>8.4 ± 0.20</td>
<td>8.6 ± 0.18</td>
<td>t = 2.73, p = 0.01</td>
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<tr>
<td>After treatment</td>
<td>6.17 ± 0.15</td>
<td>6.45 ± 0.09</td>
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<tr>
<td>Dynamics</td>
<td>0.67 ± 0.16*</td>
<td>0.14 ± 0.09</td>
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<tr>
<td>Triglycerides level (mmol/L)</td>
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<tr>
<td>Before treatment</td>
<td>1.66 ± 0.11</td>
<td>1.84 ± 0.08</td>
<td>t = 2.11, p = 0.01</td>
</tr>
<tr>
<td>After treatment</td>
<td>1.28 ± 0.05</td>
<td>1.5 ± 0.03</td>
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<tr>
<td>Dynamics</td>
<td>0.38 ± 0.05*</td>
<td>0.65 ± 0.05*</td>
<td></td>
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<tr>
<td>HDL levels</td>
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<tr>
<td>Before treatment</td>
<td>1.06 ± 0.02</td>
<td>1.15 ± 0.03</td>
<td>t = 3.77, p = 0.001</td>
</tr>
<tr>
<td>After treatment</td>
<td>1.27 ± 0.04</td>
<td>1.15 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>Dynamics</td>
<td>0.16 ± 0.03*</td>
<td>0.65 ± 0.03*</td>
<td></td>
</tr>
<tr>
<td>LDL levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>2.77 ± 0.05</td>
<td>2.81 ± 0.08</td>
<td>t = 2.78, p = 0.01</td>
</tr>
<tr>
<td>After treatment</td>
<td>2.45 ± 0.02</td>
<td>2.74 ± 0.08</td>
<td></td>
</tr>
<tr>
<td>Dynamics</td>
<td>0.32 ± 0.01*</td>
<td>0.65 ± 0.07</td>
<td></td>
</tr>
</tbody>
</table>

* Significant dynamics during treatment

The level of pain has been assessed by visual analog scale (VAS) at rest and during walking and the total index was calculated in the Western Ontario and McMaster Universities Arthritis Index (WOMAC). Data is represented in Table 2.

**Table 2.** Dynamics of clinical manifestations of OA after weight loss

<table>
<thead>
<tr>
<th>Index</th>
<th>Group 1</th>
<th>Group 2</th>
<th>The reliability of differences between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 18</td>
<td>n = 62</td>
<td></td>
</tr>
<tr>
<td>Pain intensity at rest according to VAS (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>38.0 ± 4.98</td>
<td>39.9 ± 4.09</td>
<td>t = 1.06, p = 0.02</td>
</tr>
<tr>
<td>After treatment</td>
<td>24.7 ± 2.52*</td>
<td>15.7 ± 3.51*</td>
<td></td>
</tr>
<tr>
<td>Dynamics</td>
<td>12.3 ± 2.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain intensity while walking according to VAS (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>79.8 ± 3.34</td>
<td>61.28 ± 3.91</td>
<td>t = 3.54, p = 0.001</td>
</tr>
<tr>
<td>After treatment</td>
<td>33.5 ± 2.97</td>
<td>18.8 ± 2.88</td>
<td></td>
</tr>
<tr>
<td>Dynamics</td>
<td>33.5 ± 2.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total index for WOMAC (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>989.17 ± 70.5</td>
<td>1061.5 ± 70.8</td>
<td>t = 3.82, p = 0.001</td>
</tr>
<tr>
<td>After treatment</td>
<td>402.7 ± 23.5</td>
<td>648.5 ± 21.8</td>
<td></td>
</tr>
<tr>
<td>Dynamics</td>
<td>380.3 ± 53.5*</td>
<td>33.5 ± 15.8*</td>
<td></td>
</tr>
</tbody>
</table>
In analyzing the parameters before and after treatment, it should be noted that we observed significant decrease in the severity of the clinical manifestations of OA (decrease of the level of pain on the VAS scale at rest and during walking, total score on the WOMAC), visfatin level, CRP, and glucose levels and lipid profile in the 1st group of patients. These data proves that obesity may be an important risk factor for OA progression. As a result, weight loss results in decreasing metabolic disorder severity. In the second group of patients we have seen a decrease in all the parameters, but a significant difference has been observed only in the level of CRP, level of pain at rest and during walking according to VAS scale and total index on the WOMAC. However, patients with weight loss over 5 kg had significantly greater positive dynamics of clinical parameters than in the second group without weight loss.

This fact is probably explained by the decreased activity of inflammatory process after OA therapy and weight reduction. Lack of significant changes in the second group may be due to partial compliance with the recommendations.

**Conclusion:** As a result of our study patients with OA with weight loss of more than 5 kg had more obvious pain relief than patients with the original weight. At the same time a significant improvement has been seen in carbohydrate and lipid metabolism. These findings suggest that there is a possible role of visfatin in the pathogenesis of osteoarthritis. All patients with OA with a BMI over 25 kg / m² are recommended to lower their weight to decrease the mechanical stress on the joints, and also to reduce the severity of inflammation and metabolic disorders.

The study is part of the planned research work of the institution, financed by the Federal Agency of Russian scientific organizations and does not contain any conflict of interest.

**REFERENCES**


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Спонтанни спондилодисцити - клинично протичане, хирургично лечение и изход от лечението при 25 пациенти

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България

РЕЗЮМЕ

ЦЕЛ: Да се представи клиничното протичане и хирургичното лечение при пациенти със спонтанни спондилодисцити.


РЕЗУЛТАТИ: Средната възраст на пациентите е 53.92 години. (95% CI 46.96 - 60.8) При всички болни заболяването е дебютирало с възникване на болки във връзка със спонтанните болки и слабост в краката. Продължителността на симптомите при 19 болни (76%) е варирана между 30 и 120 дни. Неврологичен дефicit е установен при 22 болни (88%), като при 21 пациенти (84%) локализацията е в лумбо-сакралната област. От оперираните 24 пациенти при 13 е осъществена само декомпресия на коренчета и консна опашка; при 10 е извършена и задна транспедикуларна стабилизация. Починал е един пациент (4%). Инфекциозният причинител е изолиран при 10 болни (40%).

ЗАКЛЮЧЕНИЕ: При пациента с прогресиращ или изразен неврологичен дефicit вследствие хематогенно възникнал спондилодисцит хирургичното лечение е метод на избор. То позволява декомпресия на невралните структури, корекция на гръбначния деформитет, последваща стабилизация и бърза мобилизация на пациентите.

КЛЮЧОВИ ДУМИ: спондилодисцит, болки в кръста, хирургично лечение.
Spontaneous spondylodiscitis – clinical development, surgical treatment and outcome in 25 patients

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¹Department of Neurosurgery, Faculty of Medicine, Medical University of Plovdiv, Bulgaria
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ABSTRACT
AIM: To present the clinical course, surgical; treatment and outcome in patients with spontaneous spondylodiscitis.

MATERIAL AND METHODS: A retrospective study of 25 patients (18 male, 7 female) who were diagnosed and treated for spontaneous spondylodiscitis has been conducted at the Clinic of Neurosurgery, St George University Hospital, Plovdiv, Bulgaria between 2006 and 2015.

RESULTS: Patient’s mean age was 53.92 years (95% CI 46.96 - 60.8). Back pain was present in all cases; 22 patients suffered from additional pain and weakness in the legs. Duration of symptoms in 19 patients (76%) varied between 30 and 120 days. Focal neurological deficit was registered in 22 cases (88%); in 21 cases (84%) the infection was localized in the lumbo-sacral region. Twenty-four patients were surgically treated; in 13 cases only decompression of the cauda equine and/or its nerve roots was performed; in 10 cases a combination of decompression and transpedicle screw fixation was performed. One patient died (4%). Infectious agent was isolated in 10 patients (40%).

CONCLUSION: Surgery is the treatment of choice in patients with progressive severe focal neurological deficit caused by hematogenous spondylodiscitis. It allows adequate decompression of the involved neural structures, correction and stabilization of spinal deformity and faster mobilization of patients.

KEYWORDS: Spondylodiscitis, back pain, surgical treatment

INTRODUCTION:
Spondylodiscitis is a rare disease comprising 2%-7% of all cases with pyogenic osteomyelitis. Its incidence varies from 1/100 000 to 1/250 000 per year [1,4]. The disease develops as a primary inflammatory process of one or more discs (discitis) which later affects adjacent vertebral bodies (spondylitis) and neural structures. The disease can follow acute or chronic course but the lack of specific symptoms often leads to delayed diagnosis with potentially high morbidity and mortality [11]. The incidence of occurrence is higher in older patients and patients with compromised immune system as a result of immunosuppressive therapy, chronic inflammation, kidney failure, alcohol or drug abuse, AIDS, diabetes, etc. [2,5].

The aim of this study is to establish the wide spectrum of spondylodiscitis types, including its clinical manifestation, risk factors, paraclinical findings that allow precise diagnosis and define the timing and type of treatment.

MATERIAL AND METHODS
A retrospective study of 25 cases with clinical and neuroimaging data suggesting spontaneous spondylodiscitis was conducted (18 male and 7 female, aged between 20 and 80 years, mean age 53.92 (95% CI 46.96 - 60.88)). The patients were
treated in the Clinic of Neurosurgery at the St George University Hospital, Plovdiv, Bulgaria for a period of 10 years (2006-2015). Medical files, paraclinical findings, imaging studies and operative protocols were thoroughly reviewed. Special attention was payed to the initial symptoms, the clinical presentation upon admission, the presence of concomitant diseases, the localization and number of the affected vertebrae, the inflammatory serum markers and microbiological results, the timing and the type of surgical intervention.

**Clinical presentation**

The clinical symptoms are summarized in Table 1. In 11 cases (44%) the disease debuted with back pain; in 9 (36%) with pain in the low back and the legs; in the last 5 (20%) cases there was low back pain and leg motor weakness. In 19 (79%) cases the duration of the initial symptoms varied between 30 and 120 days. Only 3 cases there had no neurological deficit upon hospital admission.

**Diagnostics**

The laboratory tests showed elevated levels of C-reactive protein (CRP) in all cases; leukocytosis was present in 13 (52%) cases, accelerated erythrocyte sedimentation rate (ESR) in 24 (96%) cases, from which 18 cases had ESR values between 60 and 120 millimeters (Table 1).

Plain spine radiographies showed deformations in 8 cases. Five of them had narrowing of the affected disc and irregularity of the endplates of the adjacent vertebrae, and 3 cases had a fractured vertebra. (Fig. 1).

<table>
<thead>
<tr>
<th>Table 1. Symptoms and paraclinical data upon admission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>Lower back mid or back pain</td>
</tr>
<tr>
<td>Radicular pain</td>
</tr>
<tr>
<td>Fever &gt;39°C</td>
</tr>
<tr>
<td>Peripheral motor deficit</td>
</tr>
<tr>
<td>Partial or complete cauda equina syndrome</td>
</tr>
<tr>
<td>Inferior central paraesthesia</td>
</tr>
<tr>
<td>Inferior central paraplegia</td>
</tr>
<tr>
<td>Loss of bladder control</td>
</tr>
<tr>
<td>Elevated CRP levels</td>
</tr>
<tr>
<td>Leukocytosis</td>
</tr>
<tr>
<td>Accelerated ESR</td>
</tr>
</tbody>
</table>

Computed tomography (CT) scan was performed in 13 cases. The diagnosis was established only by CT in 7 cases. Magnetic resonance imaging (MRI) was used in 17 cases - all of them showed the typical signs for this disease (Fig.2 and 3).

**Fig. 1.** Lateral and AP spondylographies demonstrating endplate destruction of L3-L4 disc.

**Fig. 2.** CT: A) axial view; B) sagittal reconstruction; C) 3D reconstruction - narrowing of L2-L3 disc space and destruction of the adjacent endplates.

**Fig. 3.** MRI of the lumbar spine: A) Sagittal T1 view - hypointensity in L3-L4 segment; B) Sagittal
T2 view - hyperintensity in the same region and presence of epidural collection (white arrow); C) axial view - epidural abscess (white arrows) and inflammation of the left intervertebral joint and the paravertebral space (black arrow).

Anatomical distribution

The anatomical distribution is presented in Fig. 4. Two spinal levels were affected in 22 cases (88%), 3 spinal levels - in 1 case (4%), one spinal level - in 2 cases (8%). In 7 cases the spondylodiscitis was combined with epidural abscess. The epidural abscess was located ventrally to the level of the affected vertebrae in 5 cases; while in the other 2 cases the abscess occupied the whole extradural space spreading beyond affected segments.

Fig. 4 Anatomical distribution of spondylodiscitis (thoracic, thoraco-lumbar, lumbar, lumbo-sacral)

Concomitant diseases

In five cases (20%) we registered diabetes as the main predisposing factor for inflammation. Three out of these 5 cases had additional high arterial blood pressure. One case suffered from cirrhosis and chronic nephritis; and one case was with ischemic heart disease. Other concomitant diseases included chronic kidney failure (two cases), toxic hepatitis (one case), carcinoma (two cases), Fallot’s tetralogy, thrombophlebitis (two cases), coxarthrosis and gonarthrosis (one case), obesity (four cases), ischemic heart disease (six cases), psoriatic arthritis (one case), and methadone therapy (two cases). In six cases (24%) there were no evident concurrent diseases.

Source of infection

Despite the careful anamnestic and clinical examination, in 20 cases (80%) no source of infection could be established. In 5 cases we found: dermal sinus, previous surgery of perforated bowel diverticulum with abscess, bilateral pneumonia, previous surgery for abscess in the gluteal region, previous surgery for mesenteric thrombosis.

Cause of infection

The successful treatment of spinal infections is directly connected to the susceptibility of the causative microorganisms to antibiotic therapy. In all cases the serological tests were negative. Figure 5 shows the isolated microorganisms from material collected during the surgeries (pus, bone and disc fragments).

Fig. 5 Isolated infectious agents

Surgical treatment

All patients in our study underwent surgical treatment, except one, who refused to sign consent. In 13 cases (54%), the surgical intervention was performed as an emergency due to the presence of acute and rapidly progressing neurological deficit. In the rest of the cases the surgery was planned. The antibiotic therapy was applied in accordance with the results from the microbiological testing. In cases with negative microbiology we initiated treatment with parenteral treatment with combination of broad-spectrum antibiotics for 14 days, followed by oral intake for 1 to 2 months.

In all of the patients that underwent surgery, we used posterior midline approach. The aim of the surgical treatment was to achieve decompression of the neural structures, removal of necrotic tissues and evacuation of epidural collections where present and obtaining material for microbiological examination. In the cases with lumbaradiculagia we performed only debridement and decompression of the affected roots and the cauda equina via interlaminar approach at one or more levels (Table 2).

Table 2. Surgical interventions

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Removal of dermal sinus and epidural abscess</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Decompression and posterior transpedicular stabilization</td>
<td>10</td>
<td>42</td>
</tr>
<tr>
<td>Interlaminar approach, discectomy and nerve root(s) and cauda equina decompression</td>
<td>11</td>
<td>46</td>
</tr>
<tr>
<td>Laminectomy, nerve root and cauda equina decompression</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>
In the cases with acute spinal instability we also performed posterior transpedicle screw fixation (Fig. 6)

Fig. 6  A) Preoperative MRI (Sagittal T2 view) - spondylodiscitis affecting L2-L3 segment with a partial destruction of L3 vertebral body;  B) and C) Postoperative spondylographies (AP and lateral) - posterior transpedicular stabilization and proper alignment of the segment

**Postoperative outcome**

The mean hospital stay was 23 days (from 7 to 60 days). Twelve of the patients had a varying degree of motor deficit upon admission; one case was with inferior paraplegia, 3 cases - with inferior paraparesis; 5 cases with either complete or partial cauda equina syndrome; three with a paresis of peripheral nerves. The motor deficit was worsened postoperatively in 11 cases; one patient died due to a pulmonary embolism (Table 3).

**Table 3. Treatment outcome (measured by MRCS)**

<table>
<thead>
<tr>
<th>SCORE</th>
<th>Preoperative period: number of patients</th>
<th>Postoperative period: number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1/5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2/5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>3/5</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>4/5</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>5/5</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

The remaining 13 cases that manifested with lumbalgia and radicular symptoms experienced significant improvement.

**Discussion**

According to most authors spontaneous spondylodiscitis is a disease mostly found in elderly people and in people who suffer from concurrent diseases that are risk factors for development of infection [1-5,11,15]. The present study confirms that the disease may also be found in younger people and men are three times more likely to be affected than women [4,19]. Despite the fact that seven of our patients (28%) are aged below 35, the mean age of our group is 53.92 (95% CI 46.96 – 60.88). The presence of risk factors is not mandatory - 8 of our patients (32%) are relatively young and have no concomitant diseases.

The period between the onset of the disease and the diagnosis varies between 1 and 6 months [4,10,19]. This is due to a variety of reasons such as the diffuse and non-specific initial symptoms (vertebralgia), the absence of infectious syndrome and the fact that symptoms are being wrongly interpreted as a result of spinal degenerative disease that is treated conservatively without the use of imaging studies [4,15]. In 19 of our cases (76%) the time between the onset of the initial symptoms and the diagnosis varies between 30 and 120 days. This contributes for the spread of the infection to the epidural space that can cause neurological deficit. Such deficit is found in 22 (88%) cases in our study (55% with motor deficit; 45% with sensory deficit).

A distinctive symptom of patient suffering from spondylodiscitis is the back and/or the lower back pain, with or without radicular involvement [12,15]. All patients in our group suffered from lower back or back pain of variable intensity while radiculalgia is present in 22 cases (88%). Fever more than 38°C was registered in 4 cases, while one patient had fever > 370°C upon admission.

The presence of leukocytosis, accelerated ESR and elevated CRP levels depend on the stage of the disease. CRP and ESR are sensitive inflammatory markers that were found beyond normal limits in 100% and 92% of our cases, respectively.

**Imaging**

Plain spine radiography is the first imaging tool that is used for patients suffering from back pain. In the early stages of the disease this test is usually negative because there are no deformations in the structure of the spinal column [20]. At a later stage some non-specific alterations can be observed.
such as narrowing of the intervertebral disc with irregularity of the vertebral endplates that can also be caused by degenerative or neoplastic process. We share similar findings.

CT scanning can better demonstrate bone alterations typical of spondylodiscitis [20]. The contrast enhancement provides better visualization of existing epidural or paravertebral abscess [7].

MRI is the diagnostic procedure of choice when spondylodiscitis is suspected [19]. It examines larger segments of the spinal column in three planes and can detect distant spread of infection. Contrast enhancement increases its sensitivity in detection of epidural abscess [9]. Generally, the acute phase of the disease is characterized by hypointensity seen on T1 sequences with destruction of the affected endplates and subchondral zones of the adjacent vertebra and hyperintensity on T2 sequences in the same regions [9].

The most common localization of the infection is a matter of debate in the literature. Lee et al. pointed out that the most commonly affected region was the thoracic spine (52%) followed by the lumbar spine (43%) [14]. Karadimas et al. reported that the lumbar spine was affected in 84% of the cases while the thoracic spine was affected in 58% versus 28% for the thoracic region [16]. Our results showed that the lumbo-sacral region was affected in 84% of the cases whereas the thoracic in 38% of the cases [13]. McHenry et al. conducted large retrospective study of 255 patients suffering from spondylodiscitis and found that the lumbo-sacral region had been affected in 58% versus 28% for the thoracic region [16]. Our results showed that the lumbo-sacral area was affected in 84% of the cases while the thoracic region in only 12% of the cases.

There is no consensus about the most optimal treatment strategy for spinal infections because there are no published large randomized trials discussing the results from the different treatment regimens [5, 12]. Conservative treatment is applied in high risk patients with mild clinical complaints and lack of spinal deformities [16]. It is preferred in elderly patients who are in poor somatic status. The main disadvantages of this treatment is the selection of appropriate antibiotics (serological tests are usually negative) and the long immobilization period necessary to achieve vertebral fusion of the affected spinal segment [7, 20, 14].

Emergency surgery is undertaken in cases with severe neurological deficit, spinal instability and deformity, presence of epidural abscess or imaging data suggesting neoplastic process [7, 19, 20]. Elective surgery is applied in cases with intractable pain and failure of conservative treatment [7, 19, 20]. The goals of the surgical treatment are decompression of the neural structures, obtaining of samples for microbiological testing, last but not least, reconstruction and stabilization of the affected segment.

The surgical treatment allows more effective elimination of the infectious complications and faster mobilization of the patients [7]. Posterior midline approach is usually used in the treatment of thoracic and lumbar spondylodiscitis which allows transpedicle screw fixation and stabilization of the affected segment that does not increase the incidence of infection recurrence [7, 8].

Blood culture examination provides the fastest and least invasive method for obtaining a bacteriological diagnosis but this test is positive in 34% to 70% of the cases [12, 15, 19, 20]. In all cases from our series the serological tests were negative. Nowadays, many authors recommend percutaneous bone biopsy under CT guidance to isolate the infectious agent followed by specific antibiotic treatment [6, 18]. Almost all of our patients had acute lumbalgia and neurological deficit that necessitated surgical intervention and obtaining of sufficient samples for microbiological examination. We managed to isolate the infectious agent in only 10 cases. We consider that this is due to the chronic phase of the infection as well as to inadequate probe handling and prolonged transportation. Staphylococcus aureus was the most commonly isolated agent which was also observed by others [15].

The prognosis of spondylodiscitis before the antibiotic era was poor but even today it can be potentially fatal [5]. The length of hospital stay varies between 30 and 57 days and mortality rate is between 2% and 17% [3-5]. When the time interval between the disease onset and the diagnosis is greater than 60 days the chance for complete neurological recovery is minimized [7, 15, 19]. In 16 of our cases the time period between disease debut and diagnosis was more than two months and none of these patients fully recovered within the hospital stay as measured by the Medical Research Council Scale (MRCS).

Conclusion

Our study shows that spondylodiscitis should be suspected in every case with persistent back pain, history of fever, paraclinical data for leukocytosis, accelerated ESR and elevated CRP. This is especially valid for patients suffering from diabetes mellitus or other concurrent diseases that present risk factors for infection. The use of MRI contributes to earlier diagnosis prior to development of neuro-
logical deficit and allows visualization of the entire spinal column in three planes. Early diagnosis helps to avoid surgery and prolonged hospital stay and immobilization.

REFERENCES:

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Primary Cutaneous T-cell Lymphoproliferative Disease and Therapy-related Acute Myeloid Leukemia in a Patient, Treated for Non-metastatic Breast Cancer – a Case Report with Review of Literature.

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²Department of Dermatology, Military Medical Academy, Sofia;
³Laboratory of Cytogenetics, Military Medical Academy, Sofia;
⁴Laboratory of Immunology, Military Medical Academy, Sofia, Bulgaria
Първично кожно Т-клетъчно лимфопролиферативно заболяване и свързана с терапията остра миелоидна левкемия при пациентка, лекувана по повод неметастазиращ карцином на гърдата – клиничен случай с преглед на литератураната.

А. Недева¹, В. Матеева², И. Киндеков¹, И. Николов¹, Н. Петкова¹, Ю. Райнов¹, Л. Митев³, А. Асенова³, Е. Викентиева⁴, Р. Владимирова⁴  
¹Клиника Хематология, ВМА-София; ²Клиника Дерматология, ВМА-София; ³Цитогенетична лаборатория, ВМА-София; ⁴Лаборатория по имунология, ВМА-София

РЕЗЮМЕ

Прилагането на адювантна химиотерапия и лъчетерапия доведе до удължаване на преживяемостта при много от пациентите с карцином на гърдата. Мултимодалното лечение обаче може да повиши риска от развитие на свързани с терапията неоплазии. Представяме случай на първично кожно Т-клетъчно лимфопролиферативно заболяване и свързана с терапията остра миелоидна левкемия след химио- и лъчетерапия по повод неметастазиращ карцином на гърдата. Прегледът на литературата, който направихме, доведе до заключението, че поява на няколко злокачествени заболявания в един пациент вероятно отразява генетична предиспопзисия към множествени неоплазии, но е възможно и двата малигнени хемопатии да са свързани с терапията на солидния тумор. Представените от нас случаи подкрепя нуждата от стриктно проследяване на такива пациенти след химио- и лъчетерапия.  

КЛЮЧОВИ ДУМИ: карцином на гърдата, мултимодално лечение, лимфопролиферативно заболяване, свързана с терапията левкемия.
**ABSTRACT**

The use of chemotherapy and radiotherapy in the adjuvant setting has improved survival for many patients with breast cancer. Multimodality treatment however can lead to increased risk of developing therapy-related malignancies. We present a case of primary cutaneous T-cell lymphoproliferative disease and therapy-related acute myeloid leukemia after chemo- and radiotherapy for non-metastatic breast cancer. The literature review we performed lead us to the conclusion that such clustering may represent genetic predisposition to multiple malignancies or the hematologic neoplasms may be therapy-related. Our case report supports the need of strict surveillance of such patients after chemo- and radiotherapy.

**KEYWORDS:** breast cancer, multimodality treatment, lymphoproliferative disease, therapy-related acute leukemia.

**INTRODUCTION**

Breast cancer (BC) is the most frequent malignancy among women. Early detection by mammography screening and improvement of therapeutic options have increased breast cancer survival rates. This makes follow-up and monitoring for late side effects of cancer treatment particularly important. The risk of developing a secondary malignancy after breast cancer treatment is significantly higher than for the general population. We present a case of primary cutaneous T-cell lymphoproliferative disease (LPD) and therapy-related acute myeloid leukemia (t-AML) occurring after chemo- and radiotherapy for non-metastatic BC.

**CASE REPORT**

A 68 year old woman presented to our department with two erythematous plaques, involving her back. She had consulted a dermatologist and underwent skin biopsy with the following histology report: primary cutaneous CD4+ small-/medium-sized pleomorphic T-cell lymphoma (Figure 1).

Past medical history included right mastectomy and axillary lymph node dissection 6 years ago for a T2N0MO invasive lobular carcinoma which was grade 2 and hormone receptor positive. She received pre- and postoperative chemotherapy (CNF regimen □ Cyclophosphamide, Mitoxantrone and 5-Fluorouracil), followed by a 5-week course of radiotherapy and 5 years of hormonal therapy.

The initial lymphoma staging confirmed cutaneous involvement only and she was treated with local radiotherapy with complete response (CR) and 6 months disease-free survival. She relapsed with multiple lesions on her truncus. After histologic confirmation she received single-agent chemotherapy □ Methotrexate (MTX) 15 mg/m2 weekly for one year.

On a scheduled visit she presented with anemia (Hb 78 g/l), thrombocytopenia (platelets 72 G/l) and marked leukocytosis (121 G/l). The peripheral blood smear showed 80% monoblasts and the bone marrow (BM) was hypercellular, totally infiltrated with monoblasts (Figure 2). The surface blast immunophenotype was: CD45+ low, CD34+, CD117+/-, CD14-, CD64-, CD13-, CD10-, CD15-, CD3-, CD5-, CD2-, CD7+/-, CD4+, CD36+, HLA-DR+, TdT-, MPO-. Conventional cytogenetic analysis, using direct and 24-hour unstimulated cultures, revealed a pathologic clone with multiple numerical and structural abnormalities in 25% of the analyzed metaphases: 46, XX, add(1)(p22), add(2)(q31), add(5)(q22), del(6)(q21q25), del(7)(q22q36), -10, -15, +2mar[15]/46,XX. In the cytogenetic report del(7q) was characterized as the major abnormality, associated with the pathogenesis of the disease. According to WHO 2008 classification of myeloid neoplasms, a diagnosis of therapy-related AML (t-AML) was made.

Differential diagnosis included relapsing NHL with a similar immunophenotype and familial myelodysplastic syndrome. Conventional cytogenetic analysis revealed normal female karyotype. Cerebrospinal fluid (CSF) however was positive for blast cells, despite the lack of neurologic symptoms (Figure 3). A second cycle of the same induction regimen was performed, combined with intrathecal chemotherapy twice weekly until lumbar puncture was negative for blast cells. Due to delayed hematologic recovery bone marrow aspirate showed less than 5% blast cells. Marrow flow cytometry detected 3.3% monoblasts with the initial phenotype and 1% promonocytes. Metaphase cytogenetics revealed normal female karyotype. Cerebrospinal fluid (CSF) however was highly positive for blast cells, despite the lack of neurologic symptoms (Figure 3). A second cycle of the same induction regimen was performed, combined with intrathecal chemotherapy twice weekly until lumbar puncture was negative for blast cells. Due to delayed hematologic recovery the patient developed severe intestinal infection, which lead to hepatic failure, hepatorenal syndrome and resulted in death.

**DISCUSSION**

Treatment for non-metastatic BC may be the cause of second malignancies in long-term survivors, depending on treatment modality. In one study estimating the risk of a second malignancy after adjuvant treatment for BC, greatest increases in risk were found for leukemia, ovarian and cervical/endometrial cancer. The increase in leukemia was most strongly related to chemotherapy and that in gynecological cancers to hormone therapy. Radiotherapy alone also had a significant,
...effect on leukemia incidence. Increased risk of sarcomas and lung cancer was found, which was attributed to radiotherapy. No increased risk was observed for malignant melanoma, lymphoma, genitourinary, thyroid or head and neck cancer (5).

Other studies also reveal that BC patients treated with adjuvant chemotherapy regimens, commonly including alkylating agents and anthracyclines, are at increased risk of developing leukemia. In a recent study adjuvant chemotherapy was associated with a cumulative 10-year incidence of leukemia of about 0.5%, which appears to be higher than previously reported (6). A population-based study found that several factors can increase the risk of AML in BC survivors: younger age at diagnosis, node positive breast cancer, dose intensity of chemotherapy, use of adjuvant radiotherapy and the concomitant use of granulocyte colony-stimulating factor (7).

Therapy-related myeloid neoplasms (t-MNs) are a distinct subgroup in the 2008 WHO classification of myeloid neoplasms and acute leukemia. They occur as late complications of cytotoxic chemotherapy and/or radiation therapy administered for a prior neoplastic or non-neoplastic disorder (9). The t-MNs may be further subdivided as therapy-related myelodysplastic syndromes (t-MDS) or t-AML, although according to the latest 2016 revision of WHO classification it is useful to think of them as a single biologic entity with overt t-AML. This category is commonly associated with unbalanced loss of genetic material, often involving chromosomes 5 and/or 7. Such cases and those with a complex karyotype have a particularly poor outcome, with a median survival time of less than one year (9). The second category (20-30% of patients) has a shorter latency period of about 1-5 years and follows treatment with topoisomerase II inhibitors. Most patients in this subset do not have a myelodysplastic phase but present initially with overt AML, often associated with balanced chromosomal translocations, frequently involving 11q23 (MLL) or 21q22 (RUNX1). Many cases fall in the categories of acute monoblastic and myelomonocytic leukemia. Patients generally have a better prognosis compared with the first group, but still median survival times are shorter than their de novo counterparts (9).

Like in our case, most patients who develop therapy-related myeloid neoplasms have received alkylating agents and/or radiation as well as topoisomerase II inhibitors, so according to 2016 revision of WHO classification a division according to the type of therapy is usually not practical and is no longer recommended (2). Our patient had received mitoxantrone, cyclophosphamide and radiotherapy 7 years before developing overt t-AML, without a MDS-phase. Her leukemia was monoblastic and cytogenetics revealed a complex karyotype with del7q. It is obvious that her t-AML had features of both of the above mentioned subsets.

Other cytotoxic agents have also been implicated to cause t-MNs, like antimetabolites and antitubulin agents (9). Hematological malignancies (lymphoma or AML) have also been reported to be secondary to MTX therapy, but are very uncommon and occurring in patients with rheumatoid arthritis treated with MTX for longer periods and with higher cumulative doses (1). According to some authors it is likely that the occurrence of AML in patients with rheumatoid arthritis in the setting of methotrexate therapy may represent just coincidence of these two diseases or an association with the primary autoimmune disease (6). In our opinion in our case the duration and cumulative dose of MTX treatment cannot result in t-AML.

While t-MNs are well-recognized consequences, therapy-related lymphomas are less well studied. An article on therapy-related lymphomas in patients with autoimmune diseases suggests that azathioprine/cyclophosphamide-related lymphomas and t-MNs might evolve through similar oncogenic pathways (3). Another study on non-Hodgkin lymphomas in women with BC found no evidence that lymphoma as a second neoplasm was therapy-induced (11).

Soon after the completion of hormonal therapy for BC our patient was diagnosed with primary cutaneous CD4+ small/medium T-cell lymphoma which was included as a provisional entity in the 2008 clas-
Histologically, these neoplasms are characterized by a proliferation of small/medium-sized lymphocytes with pleomorphic morphology, as well as an admixture of reactive lymphocytes and histiocytes (4). The cells have a T follicular helper (TFH) phenotype, but recurrent mutations as seen in nodal TFH lymphoma have not been reported. Several clinical series have been reported, revealing that clinical behavior is almost always indolent, with most patients presenting with localized disease. Systemic disease is rare, and conservative local management is sufficient in most cases. It has been suggested that this may represent a limited clonal response to an unknown stimulus, not fulfilling criteria for malignancy. The terminology in the revised classification has been modified to reflect this uncertain malignant potential, designating these cases as primary cutaneous CD4+ small/medium T-cell LPD (2). In our case the disease had was initially responsive to local radiotherapy, but due to the short duration of remission required maintenance chemotherapy. Because of the rarity of this condition there are no literature data that give us ground to assume a definitive causal relationship to the previous exposure to cytotoxic or radiation therapy.

CONCLUSION

The presented case is unique with the occurrence of a solid tumour, a lymphoproliferative disease and a myeloid neoplasm in one patient. Such clustering may represent genetic predisposition to multiple malignancies or the hematologic neoplasms may be therapy-related, which we have assumed for AML in our patient. The data from multiple studies have shown increased risk of second malignancies in women treated for BC and our case report supports the need of strict surveillance of such patients after chemo- and radiotherapy.
REFERENCES


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Задължения на резензентите
Резензентите подпомагат редактора при вземане на решение. Посредством редакционната комуникация те могат да подпомогнат автора в повишаване на качеството на статията.

Всички ръкописи, получени за рецензиране следва да се съхраняват за поверителни материали и тяхното съдържание на следва да се разкрива пред никого, освен с разрешението на редактора.
Рецензиите следва да се придържат към обективни стандарти на оценка. Лични нападки срещу авторите са неприемливи.

Критичните забележки следва да бъдат подкрепени с аргументи.

Конфликт на интереси

Непубликувани материали не могат да бъдат използвани в собствени изследвания на редактора без изричното писмено съгласие на авторите.

Авторите следва да обявят всички финансови или други съществени конфликти на интереси, които могат да окажат влияние върху интерпретацията на техните резултати. Всички източници на финансиране на проведените проучвания следва да бъдат обявени.

Етически съображения по отношение на самите изследвания: всички трудове, които отразяват експерименти с хора следва да бъдат съобразени с етическите норми и регламентации, въведени от съответния местна или регионална научна комисия и/или с Декларацията от Хелзинки, ревизия от 2000г. Експериментите с животни следва да бъдат също така съобразени със съответните норми и правила.

След положителна рецензия и одобрение на редколекцията, авторите на статията дължат заплащане в размер на 10 лв. за всяка стандартна машинописна страница, с оглед на покриване разноските по английска езикова редакция на текста и коректири.

Всички материали за списанието се изпращат на посочения адрес на редакцията:
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