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CYTOKINES AND RHEUMATOID ARTHRITIS

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Complex of symptoms of immunopathologic changes developing in the composite components of joint synovia is the basis of the pathogenesis of rheumatoid arthritis. Analysis of literature and our own findings show that in the initiation of immunopathologic disorders of this desease a special place must be given to "molecular carriers of immunity" – lymphocytes, which produce biologically active agents of wide spectrum. It has been determined that unstimulated thymus lymphocyte active products have arthritogenic potencies. This fact testifies to their important role in the pathogenesis of systemic diseases with immune disorders, particularly, at rheumatoid arthritis.

Intravascular injection of lymphocytic mediators in the knee joint causes an unpurulent inflammatory process which has many general features with human rheumatoid arthritis: hyperplastic synovitis, lymphoid follicles formation with local stimulation of lymphoid line cells on the synovial membrane, rheumatoid factor and synthesis of antibodies with pannus development

Development of dystrophic and immunopathologic changes in the urea of arthroidal cartilage is pathognomic for arthritis induced by lymphocytic mediators. This process forestalls "immune inflammation" development in the synovial membrane. That is why the destructive process of composite components of arthroidal cartilage with following development of immunopathologic process in its area is the initial factor of the pathologic changes development. The present process stimulates the course and trend of experimental arthritis which is identified by us with human rheumatoid arthritis.

Special series of experiments revealed possible mechanisms of pathological shifts development in joint synovia. In vitro condition in lymphocytic mediators it has been revealed that antigenic determinants crossly react with C-part of the parathyroid hormone. That is why the joint cartilage and bone tissue resorption processes, accompanied by ionized calcium increase in synovia and blood, testify to the presence of a factor having analogies with parathyroid effect on target-organs in the lymphocyte mediators.

To our opinion the arthritis model opens good prospects for a detailed study of lymphocyte mediators and their role in the pathogenesis of human rheumatoid arthritis.

According to the modern conceptions there are three different structural organizations of pannus. They are distinguished by correlated cells of hematogenous and histogenic lines in granulative tissue. An opinion exists that this "aggressive" tissue plays the main role in the joint destruction by rheumatoid arthritis [1]. Joint cartilage destruction by granulative tissue elements of synovial membrane takes place mainly due to hydrolytic enzymes of the monocyte-phagocytic cells of pannus.

We are of a diametrically opposite opinion, according to which the granulative tissue grows from the side of synovial membrane on a free surface of hyalinous cartilage. It is a secondary process, since it is directed towards the restoration of its integrity.

This point of view is confirmed by following facts: firstly, three types of pannus according to the dynamic development of their loose connective tissue must be considered as chronologically successive stages of granulative tissue differentiation resulting in sclerosis.

Secondly, it is known that pannus fibrous tissue on the later stages of rheumatoid arthritis development is frequently subject to "chondroidal" transformation. The process of "chondroidal" metaplasia causes fibrosis and sclerosis in the pannus tissue. We must also consider this fact in connection with formation of protective and adaptive reactions, since we know that the transformation in limits of one and the same connective tissue occurs in a concrete case owing to relative stability of cartilaginous tissue to oxygen deficit in consequence of locally developed microhemocirculatory and metabolic disorders. The new supposition brought up by us is highly grounded, for reparative-proliferative processes in their biological basis result in partial and complete structure restoration of already injured cartilage and bone tissues. These processes are mainly characterized by the stage development of connective tissue.

An absolutely different view is observed when the anatomical peculiarities of pannus development and outcome of osteofibrous tissue lead to expressed deformation and dysfunction of small and big joints of rheumatiod arthritic patients. At the same time synovial membrane can be the source of production of different biologically active substances (lymphokines, monokines, hydrolytic enzymes, immune components), rendering alternative effect on joint cartilage indirectly, through synovial fluid. However, such a mechanism is included into the general chain of immunopathologic reactions on a definite stage of rheumatoid arthritis formation, that is in the period of development of resorption processes in joint cartilage and adjacent bone.

The etiology of rheumatoid arthritis up to the present is not ascertained. Among the probable infecting agents are viruses, some bacteria, their L-forms, Mycoplasma. However, at the present there is not definite information testifying to the direct participation of microorganisms in the development of the pathological process in the affected joints. Unlike different derivates of connective tissue, including

synovial membrane, cartilage tissue is a highly favourable object for the microorganisms persistence, for despite its considerable metabolic activity, cartilaginous tissue is deprived of the possibility of mechanisms of nonspecific and specific immunological resistance in its area.

According to Denman A. joint cartilage of patients with rheumatoid arthritis is a base for virus persistence.

Our previous researches [2] have demonstrated that polyarthritic syndrome, induced in rabbits and rats by Mycoplasma fermentans is accompanied by relatively prolonged Mycoplasma persistence in the joint cartilage and destructive and immunopathologic processes of development in it. It is not excluded, that the interaction of viruses, Mycoplasma with cells of gialinous cartilage may expose "latent" antigenic determinants, causing autoimmune reaction, directed against either joint cartilage or antigen, which is peculiar both to cartilage tissue and provoking infection agent [3].

In this case antibodies must be syntetizied against the agent and cartilage tissue as well as their crossly reacting antibodies. This process may lead to the formation of immune complexes, both circulating and fixed in tissues, the beginning in the tissues of cartilage and vessels walls and causing activation of cell reaction and local antibody production. These immune complexes form with components of synovial fluid complement larger complexes, which can be phagocitized by macrophages, while the released lysosomal enzymes would support the local prolonged inflammatory process. At the same time the joint cartilage and border bone integrity violation with revealence of chondrocytes hidden antigenic determinants is supposed to be the main factor for microorganisms persistence.

In consequent study of the biological activity of lymphocytic mediators, their protein and lipid fractions [4-8] a question arises — what is the rule of endocrine disorders, connected with calcium regulated system in the pathogenesis of rheumatoid arthritis. A definite interest represents the fact that the founder of the Russian surgical endocrinology V. Oppel, who performed in 1926 operations of parathyroidectomy in patients with ankylosing polyarthritis pointed to the connection between parathyroid glands function and joint lesion character. However, in rheumatology and arthrology development later on the parathyroid glands were not investigated by special directed research.

We revealed facts which confirm the parathyroid glands participation in the infectious process in particular through lesion of the skeletal system [9]. For the first time it was determined that the famous "saprophyte" of human urogenital tract Mycoplasma fermentans induces polyarthritic syndrome development in experimental animals by means of a number of immunomorphological signs resembling human rheumatoid arthritis, which testifies to a possible ethiological role of Mycoplasma in this pathology. It is necessary to note that for polyarthritis, induced by M. fermentans, highly pathognomonic was the early drawing of the joint cartilage and border bone into the pathological process, which forestalled the development of immunopathologic changes in synovial membrane. It

is highly important that the destructive process in the subchondral and deep parts of the bone tissue, as in case of intraarticular injection to lymphocytic mediators, proceeded by the type of periosteocytic osteolysis, connected with direct influence of parathyroid hormone on target-organ. So, a single intraperitoneal injection of M. fermentans to rabbits and rats already on the second day after contagion led to expressed changes in parathyroid gland cytoarchitectonics: light-cell hyperplasia was accompanied during the first week by the increase of parathyroid hormone level, general and ionized calcium level in the blood.

For the first time A.Kennedy [10] analyzed hyperparathyroidism development at rheumatoid arthritis and showed that it causes hypercalcemia.

In Kopyova's T. monograph [11] there are facts about dystrophic changes in cartilaginous and bone tissues of joints with high activity of pathological process in small joints in patients with rheumatoid arthritis, which morphologically was typical for the parathyroid osteodystrophy process (fibrous osteodystrophy). Stecula V. and Moros N. in 1970 considered that on the definite stage of inflammatory process in synovial membrane in patients with rheumatoid arthritis in bone tissue the reparative processes intensify and are accompanied by activation of perichondrium and periostium cells. At the same time bone tissue osteolysis in its deep parts occured which, in the authors opinion, takes place as a result of activated osteoclasts penetration into the osteomedullar area.

Researches of Armenian rheumatologists [12, 13, 14] show that on the background of parathormone level increase in blood in patients with rheumatoid arthritis hypocalciemia is observed. Hypocalciemia, in the authors opinion, is connected with vitamin D deficiency in the population of Armenia.

The revealed results allowed them to base the necessity of prolonged monitoring of calcium level in blood at rheumatoid arthritis and separation of patients with firm hypocalciemia into the group of risk of secondary parathyrosis development. This recommendation is well-founded, for according to the existing hypocalciemia classification [15, 16, 17] in the early stage of the development of secondary hyperparathyrosis (variety of organic hypercalciemia in consequence of parathyroid glands hyperfunction) calcium concentration is not increased as compared to norm or even lower. It is not excluded also, that hypercalciemia at rheumatoid arthritis can also arise as a result of acid-base balance disturbance in the blood (acidosis) or endocrine disorders thyrotoxicosis, hyperthyrosis, adrenal glands failure).

It is known, that hyperparathiroid osteodystrophy is characterized by systemic osteolysis of bone structure. At the same time, with bone structures diffuse resolvation under the influence of parathormone in the resorption zones cell-fibrous tissue proliferates.

As a result total transformation of bone organ can develop in compact fibroreticular tissue [18].

At the same time rheumatoid arthritis bone tissue lesion by the type of periosteocytic and pericanalicular resorption is not a general process, but most probably has a local character, restricted mainly in periarticular parts. That is why a doubtful conception exists, according to which resorption processes in the firm joints tissues are caused by "fibrous osteodystrophy".

An opinion exists according to which bone tissue lesion at rheumatoid arthritis is constantly accompanied by osteoporosis [19, 20, 21]. In the development of systemic osteoporosis an important place is given to hormones of calcium regulating system [22, 23]. Systemic osteoporosis is not a result of parathyroidine hyperproduction, on the contrary, it is hypofunction of parathyroid glands.

Khmelnitsky and co-authors point out that hyperparathyroid osteodystrophy is characterized by systemic osteolysis of bone structure, which is erroneously marked as systemic osteoporosis.

According to [20] bones lesion by rheumatoid arthritis is almost always manifested by osteoporosis which has either a generalized character or is manifested as local periarticular osteoporosis, which is connected with direct influence of different biologically active substances—mediators of inflammation on the periarticular bone tissue.

We are far from the thought that arthrologists, immunologists, pathanatomists, endocrinologists confuse these two notions, so far as morphological findings in bone tissue testify to two diametrically contrary pathogenetic processes, caused in a certain degree by parathyroid glands hyper- and hypofunction. It is not excluded, that both processes are of not systemic, but most probably, of symptomatic local character and arise separately at concrete stages during the pathological processes development in the joints.

The obtained experimental and clinical data are clearly kept within a relatively new conception about the role of calcium regulating system in the development of initial stages of the stress-syndrome [24]. So according to the present conception, in the realization of stress syndrome, besides well known mechanism of activation of hypothalamo hypophysial-adrenal system, sympathoadrenal system, the parathyroid glands hormones are also included. The parathyroid glands are included in the stress-syndrome formation mainly in the anxiety stage, expressed by processes of light cell hyperplasia, hyperparathyroidosis and hypercalcemia.

The above mentioned facts allow us to consider from a new position different changes in the organism, which are, as a rule, induced and accompanied by condition of transitory hyperparathyrosis.

At the same time we want to note an important circumstance, which has not been regarded by immunologists, and radioimmunologists.

Firstly, the parathyroid hormone level in the blood does not testify to its biological activity, in particular, the direct influence on target-organs. Secondly, the parathyroidine concentration in fluids is defined as a rule by radioimmunologic method, often using for this aim commercial Kits sets to C-end part of parathyroidin, which is not a biologically active en

part, but rather an immunological. At the same time, the determined antigenic determinants to the C-end part of parathyroidine do not yet witness to the maintenance and all the more, activity of parathyroidine, circulating in the blood. Thirdly, the antigenic determinants to the C-end of parathormone were revealed also in supernatants of incubated intact tymocytes without their additional stimulation.

Moreover, the lymphocytic mediators had resorptive influence on bone and cartilaginous tissues. It is significant also that the resorptive influence of lymphocytic mediators at their intraarticular injection increased also the ionized calcium level in the synovia and blood, but this process was not accompanied by signs of parathyroid glands activation. It is significant that a similar agent (analogous by its biological and immunological activity) is produced not only by lymphocytes of thymus, but also is the product of monocytic secretion. So, there are given highly convincing facts about the tissue influence of IL-1 on the calcium level and bone structure of intact rats [25]. The authors have established that a subcutaneous injection of recombinant α and β IL-1 lead to the expressed and dose-dependent increase of the calcium concentration in the plasma of intact animals.

By quantitative histomorphometry of bone cuts there are clearly observed resorption processes of bone tissue. Due to the obtained facts, the authors come to an important, to our mind, conclusion, according to which defined effects of IL-1 remind a picture, developed in parathyroid hormone infusion. In favour of the important role of cytokines in the processes of cartilaginous tissue metabolism and destruction justify many researches [26, 27, 28]. It is determined that chondrocytes, stimulated by IL-1 (which is released from mononuclear cells of peripheral blood) produce IL-6, which is regarded by them as one of the mediators of cell interaction at rheumatiod arthritis.

Thus, parathyroidine high level in the blood of patients with rheumatoid arthritis does not indicate the inclusion of this hormone in the general pathological process of connective tissue systemic lesion, which expresses the periosteocytic and pericanalicular osteolysis of the bone tissue.

At present we, undoubtedly, state that the pathogenesis of rheumatoid arthritis is very complicated and multilateral. It is impossible to take into account only "provoking" factors even at concrete stages of the disease. However, the obtained results allow us to distinguish conditionally from the polycomponent endocrine and immune systems two definite integrative links (thymus and parathyroid glands) and to study them at arthritis of different genesis, including also human rheumatoid arthritis.

It is important to note, that the facts defined by us allow us to assume, that the activity of the sphere of influence of cytokines (mainly lymphocytic mediators) is not limited to the participation of immunopathologic mechanisms formation. The role of lymphocytic mediators must be considered from the point of view of their participation in physiological processes of intersystemic regulatory development,

differentiation, metabolism of parenchymatous organs, and all varieties of connective tissue.

Researches performed in the Research Center of The Yerevan Medical Institute [4, 7, 8, 29-41] have determined stress-limiting effect of the same lymphocytic mediators. In favour of our advanced conception also testify highly valuable papers [42-47]. We deliberately refrain from detailed analysis of our own and other data, concerning the physiological role of lymphocytic mediators, because these facts will be published in the near future in a special edition of collective scientific works of the Yerevan Medical Institute Research Center under the title of – "The role of lymphocytic mediators in the formation of adaptive syndrome" and in the monograph of Zilfian A. V. "Lymphocytes and adaptive syndrome".

At the same time the analysis of our own and other data allows us to give a brief interpretation of the facts, concerning arthritogenic potencies of lymphocytic mediators.

It is known that a joint represents a limited reserved system with typical peculiarities of metabolism and angioarchitectonics, owing to which intraarticular injection of lymphocytic mediators, even in "physiological" concentrations, can result in composite components of joint synovia symptom-complex, which by its principal signs reminds us of human rheumatoid arthritis.

In conditions of pathology concrete lymphocytic populations apparently produce different by the nature and spectrum of action biologically active substances, which to a certain degree cause pathological process development in joints. Highly fundamental are opinions, according to which the major part of reactions of cell-mediated immunity depends not on the lymphocytes-effectors, but most probably on the soluble products of lymphocytes-lymphokines [48].

In conclusion, we find it necessary to give a brief interpretation of arthritogenic potencies of lymphocytic mediators, their role in the pathogenesis of rheumatoid arthritis.

According to the conception, suggested by us, the dystrophic changes in the solid tissues of joints (joint cartilage, border bone) must be considered as the initial and, possibly, the starting point of the development of symptom-complex of structural and immunopathological changes in the synovia of patients with rheumatoid arthritis. We regard that at the early stages of the desease an important, or possibly determining role in the resorption process induction belongs to cytokines and, particularly, lymphocytic mediators, which are effected by short-distance principle – in the concrete cause by the direct alternative influence on the solid tissue of joints. This fact is well demonstrated by [48] :"...mediators in the zone of lesion, for example, released by infected cells, have no paramount importance for the beginning inflammatory reaction. For this purpose lymphocyte excellently fits, because it accompanies all inflammatory cell. It can be shot by mediators exactly there and exactly then, when it is all the more necessary, – in the direct proximity of the target-cell".

What are the possible ways of lymphocytic mediator resorptive effect realization on the bone and cartilaginous tissue of the joint. It is not excluded that in the initial stage of the mentioned process in "periarticular" bone tissue and, possibly, joint cartilage the circulation in the blood of lymphoid line cells occurs, which penetrate by hematogeneous and/or lymphogenic ways into the joint synovia and border bone tissue. In this case the resorption process is realized owing to the production of lymphokines by stimulated lymphocytes in synovia directly in bony basis of joints. Among these lymphokines a factor is presented, analogous by its biological influence on bone tissue with parathyroid hormone. At the same time the stimulated lymphocytes in the synovial membrane can exert direct alternative influence on its composite components, owing to production of wide spectrum of biologically active substances, including the influence of proinflammatory spectrum.

In the development of immunopathologic process on the territory of synovial membrane of patients with rheumatoid arthritis an important role must be rendered to the local formation of functionally active intercellular cooperation's [lymphocyte-neutrophilic, eozinophilic and basophilic leukocytes, lymphocyte-monocyte]. These cooperations are a function of short-distance mechanism. In the mechanism of formation and duration of (immunologic) inflammation in joints of patients with rheumatoid arthritis, in particular, further destruction of joint cartilage and subchondral bone, an important place must be given to endogenous active factors. These factors possibly are locally produced by lymphocytes which participate in the formation of follicle-like structures in the synovial membrane. Indirect confirmation of spontaneous (autogenic) stimulation of T-cells in hyperplastic synovial membrane of patients with rheumatoid arthritis is the fact of their relatively high activity and simultaneously weak response to the known mitogen F 9A [49].

In the study of rheumatoid arthritis etiology and pathogenesis it must be investigated the role of different cell association of marrow in the lesion mechanism of deep parts of (periarticular) bone tissue (spongious layer). It is determined, that the marrow like immunogenesis peripheric organs, can be a bridge-head for the persistence of viruses, bacteria, mycoplasma, separate representatives of which have mitogenic potencies as regards to lymphoid line cells. That is why, it is not excluded that the processes of periosteocytic osteolysis and/or osteoporosis in the (periarticular) bone tissue of patients with rheumatoid arthritis arise as a results of direct and/or indirect mediator influence produced by lymphocytes of marrow besides the influence of persisting microorganisms activity and degradation products on the target-organ.

Received new valuable facts about the role of cytokines in the genesis of rheumatoid arthritis are an objective reason for revision of the term Rheumatoid Arthritis [RA].

RA due to its clinical diversity and anatomical manifestations and polymorphism on separate stages of its study is called by different terms: infection nonspecific polyarthritis, chronic deformative rheumatism, chronic-evaluative polyarthritis, deformative arthritis. Some of the above,

mentioned terms have been created on the etiological principle and assume infectious genesis of this disease. At the present time there are no indisputable facts in favour of direct participation of microorganisms in the rise of RA. That is why [50] noted – "Now it is justified, that the understanding of RA as separate nosological forms, is apparently caused by different etiological factors, but united by immunopathological mechanism" [50].

To our mind, as etiological moment can be different endogenous and exogenous factors, including microorganisms, which by their taxonomic peculiarities have prolonged electoral stimulative effect on monocytic and lymphocytic line cells. For this role L-forms of bacteria, mycoplasma viruses are suitable on one hand, which owing to prolonged persistency in the organism have direct alternative effect on the joint synovia, and on the other hand, owing to the electoral mitogenic activity, participate in the processes of lymphocitic mediators and monokines secretion.

That is why all these terms do not reflect the true essence of the disease in etiological and pathogenetic aspects.

Having performed our own researches and summarizing facts we may suggest a new term for this disease based on the pathogenetic principle – "Cytokinogenetic arthritis"

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ՑԻՏՈԿԻՆՆԵՐԸ ԵՎ ՌԵՎՄԱՏՈԻԴ ՀՈԴԱԲՈՐԲԸ

Ա.Վ.Զիլֆյան

Ցիտոկինների դերը ռեւմատոիդ հոդաբորբերի առաջացման խնդրում հանդիսանում է բանավեճի առարկա: Համաձայն սեփական կոնցեպցիայի՝ հոդերի կարծր հյուսվածքների (հոդային ածառ, ենթակա ոսկրեր) փոփոխությունները հարկ է դիտել որպես սկզբնական հնարավոր է նաեւ որպես դրդող մոտենում ռեւմատոիդ հոդաբորբով տառապող հիվանդների սինովյալ միջավայրի կառուցվածքային եւ իմունաբանական փոփոխությունների սիմպտոմ–կոմպլեքսում:

Գտնում ենք, որ հիվանդության զարգացման վաղ շրջանում ռեզորբցիոն պրոցեսների խթանման մեջ կարեւոր, եթե ոչ որոշիչ դերը պատկանում է ցիտոկիններին, մասնավորապես լիմֆոցիտար մեդիատորներին, որոնք որոշակի դեպքերում ուղղակի ախտահարիչ ազդեցություն են ունենում հոդերի կարծր հյուսվածքների վրա:

Մեր եւ գրականության տվյալների վերլուծության հիման վրա, նշված հիվանդության պաթոգենետիկ անվանման առումով, առաջարկում ենք նոր տերմին, այն է՝ "Ցիտոկինոգեն հոդաբորբ":

ЦИТОКИНЫ И РЕВМАТОИДНЫЙ АРТРИТ

А.В.Зильфян

Дискутируется возможная роль цитокинов в патогенезе ревматоидного артрита. Согласно выдвигаемой собственной концепции, дистрофические изменения в твердых тканях суставов (суставный

хрящ, подлежащая кость) следует рассматривать в качестве инициального, а возможно, и пускового момента в развитии симптомокомплекса структурных и иммунопатологических сдвигов в синовиальной среде больных ревматоидным артритом. Мы считаем, что на ранних этапах развития заболевания важная, если не определяющая, роль в индукции процессов резорбции принадлежит цитокинам, и в частности лимфоцитарным медиаторам, благодаря их прямому альтерирующему влиянию на твердые ткани суставов.

На основании анализа собственных и литературных данных нами предложен новый термин для обозначения указанного заболевания, основанный на патогенетическом принципе – "цитокиногенный артрит".

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