Systemic Diseases of Connective Tissue with Autoimmunization. Rheumatism. Rheumatoid Arthritis. Systemic Lupus Erythematosus. Scleroderma. Dermatomyositis. Bechterew's (Strumpell's) disease Systemic Diseases of Connective Tissue or

Rheumatic diseases are a group of chronic diseases characterized by systemic lesion of connective tissue and blood vessels.

In their *aetiology* a significant role is played by a clinically apparent or latent streptococcic infection and the *pathogenetic* mechanisms mainly consist in allergic reactions of delayed and immediate type. There develops progressive disorganization of connective tissue –

a mucous edema,

a fibrinoid edema and necrosis,

cellular reaction (granulomatosis)

and sclerosis.

Although the pathogenesis of rheumatic diseases is of a single-type, every nosologic form has its characteristic peculiarity. In **rheumatism**, for instance, the sensitizing factor is the antibodies against the β-hemolytic streptococcus of A-type that have affinity to antigens of cardiac connective tissue. That is why rheumatism usually affects the patient's *heart*.

Rheumatoid arthritis mainly affects the connective tissue of articular capsules. Important to the pathogenesis of the disease are the immune complexes where the antibodies are immunoglobulins of various types (Ig M, Ig G, Ig A).

In *systemic lupus erythematosus* the DNA metabolism is disturbed and antibodies are produced against the components of the nucleus and the cytoplasm – DNA, RNA, histones, nucleoproteins. This causes polymorphic changes in many organs and tissues but mainly in *skin, vessels, kidneys and heart.*

Systemic scleroderma is characterized by sclerotic and atrophic changes of *skin*. Deranged synthesis of collagen is considered to be the decisive factor for scleroderma development.

Periarteritis nodosa is defined by a complex immune mechanism of *arterial lesion* of small and medium calibre which leads to secondary transformations of internal organs. It is considered that the fibrinoid necrosis of middle coat of blood vessels causes the development of proliferative reaction of cells in the outer coat, which is followed by sclerosis and formation of nodes.

Rheumatism

is a chronic disease with prevailing lesion of heart and blood vessels.

Its progression is undulating, periods of exacerbation alternate with remissions.

Its development is associated with β-hemolytic streptococcus of A-type. However, rheumatism cannot be regarded as a simple streptococcic infection.

Penetrating the body through tonsils, streptococci release toxins and cause in the places of invasion cell destruction and inflammation that usually manifests itself in tonsillitis.

The toxins and cell destruction products are the antigens against which antibodies are produced. Recurrent exacerbation of tonsillitis serves as a starting point for the development of the disease.

Four stages of connective tissue disorganization are observed in the development of rheumatism –

mucous edema,

fibrinoid changes,

granulomatosis and

sclerosis.

Mucous edema

is surface and reverse disorganization of connective tissue characterized by intensified metachromatic reaction to glucosaminoglycanes and hydration of basal substance.

Mucous edema

For a clinician it is important to know that this phase is reversible.

Early diagnosis and beginning of treatment may bring complete recovery.

Fibrinoid changes

(swelling and necrosis) are irreversible.

They are characterized by homogenization of collagen fibres that get impregnated with plasma proteins, including fibrin.

The stage of *granulomatosis* manifests itself morphologically inflammatory reaction of cells. It was first described in the form of nodular masses in heart stroma by *Aschoff* (1904) and in 1930 V.*Talalayev* singled out three phases in the development of rheumatic granuloma –

- alterative-exudative,
- proliferative and
- sclerotic.

Correlating them to clinical data he showed that the whole cycle of granuloma development lasts for 4-6 months.

granulomatosis

The *alterative-exudative phase* is characterized by accumulation of macrophages around the fibrinoid necrosis focus, which transform into big cells with a hyperchromic nucleus. Such granuloma is called "floriferous". It indicates an acute process going on.

In the *proliferative phase* the cells become elongated, there appear fibroblasts and the quantity of fibrinoid masses decreases.

The "fading granuloma" develops.

It indicates the attenuation of the process.

In the *phase of sclerosis* the fibroblasts substitute the fibrinoid necrosis zone, and argyrophil and collagen fibres are synthesized.

The granuloma assumes the properties of a scar.

This indicates the remission of the disease.

In typical progression of rheumatism it is the heart that is affected first and foremost. There develops endocarditis, myocarditis, less often – pericarditis.

Sometimes one can observe acute polyarthritis characterized by swelling of big joints, quick passage from one joint to another, and restoration of their functions during remission.

Chorea, erythema annulare, formation of hypodermic nodes that used to be typical of rheumatism, is relatively rare nowadays.

According to localization, endocarditis can be *valvular* (valvulitis),

chordal and

parietal.

In most cases the rheumatic process affects the *mitral* and the *aortic valve*.

☐Depending upon the prevailing alterative or regenerative process, one distinguishes between four types of rheumatic valvular endocarditis:
a)diffuse endocarditis
☐characterized by diffuse mucous edema of connective tissue without endothelium lesion;

acute rheumatic fever
☐The small verrucous vegetations seen along the closure line of this mitral valve. These warty vegetations average only a few millimeters and form along the line of valve closure over areas of endocardial inflammation. Such verrucae are too small to cause serious cardiac problems.
b) acute verrucous endocarditis
☐defined by fibrinoid transformation of connective tissue and endothelium desquamation with accumulation in the places of lesion of thrombotic masses in the form of warts
c) fibroplastic endocarditis
☐that develops as a result of the above mentioned forms and is characterized by excrescence of the newly formed connective tissue, emboly of blood vessels and regeneration of epithelium; the valve is thickened and transformed by scars which causes its deficiency (acquired valvular disease);
Stenosis of mitral valvular

☐The heart has been sectioned to reveal the mitral valve as seen from above in the left atrium. The mitral valve demonstrates the typical "fish mouth" shape with chronic rheumatic scarring. Mitral valve is most often affected with rheumatic heart disease, followed by mitral and aortic together, then aortic alone, then mitral, aortic, and tricuspid together.

☐In time, chronic rheumatic valvulitis may develop by organization of the acute endocardial inflammation along with fibrosis, as shown here affecting the mitral valve. Note the shortened and thickened chordae tendineae.
d) recurrent verrucous endocarditis

☐characterized by recurrent disorganization of the newly formed connective tissue, endothelium lesion and fibrin deposition due to sclerosis and hyalinosis of the valve; this process indicates a recurrent rheumatism attack.
Myocarditis
☐is a constant manifestation of rheumatism. Three forms of it are singled out:
☐a) granulomatous, characterized by the presence of “floriferous”, “fading” and sclerotic rheumatic granulomas in perivascular connective tissue;
☐b) diffuse exudative interstitial myocarditis characterized by edema, hyperaemia and considerable infiltration of intersticium with lymphocytes, histiocytes, neutrophils and eosinophils, and solitary Aschoff-Talalayev granulomas;
☐c) focal exudative interstitial myocarditis that manifests itself in slight focal infiltration of intersticium with lymphocytes, histiocytes and neutrophils. Under favourable conditions myocardite develops into cardiosclerosis.

☐Microscopically, acute rheumatic carditis is marked by a peculiar form of granulomatous inflammation with so-called "Aschoff nodules" seen best in myocardium. These are centered in interstitium around vessels as shown here. The myocarditis may be severe enough to cause congestive heart failure.
Aschoff nodule
☐The most characteristic component is the Aschoff giant cell. Several appear here as large cells with two or more nuclei that have prominent nucleoli. Scattered inflammatory cells accompany them and can be mononuclears or occasionally neutrophils.

☐Another peculiar cell seen with acute rheumatic carditis is the Anitschkow myocyte. This is a long, thin cell with an elongated nucleus.
Pericarditis

☐is a sort of serous, serofibrinous or fibrinous exudative inflammation. It often ends with the formation of adhesions.
☐Obliteration of pericardial cavity and calcification of the formed connective tissue may also occur (stone heart).

☐This diagram depicts the appearance of a serous pericarditis. The amount of inflammation is minimal, so no exudation of fibrin occurs. The dark stippled dots in the yellow fluid and on the epicardial surface represent scattered inflammatory cells. Serous pericarditis is marked by fluid collection. Rarely, the fluid collection may be large enough to cause tamponade.
Serous Pericarditis

☐This diagram depicts the appearance of a fibrinous pericarditis. The red-pink squiggly lines extending from the epicardial surface into the yellow fluid represent the strands of fibrin. This type of pericarditis is typical of uremia with renal failure, underlying myocardial infarction, and acute rheumatic carditis.

☐This is an example of a fibrinous pericarditis. The surface appears roughened from the normal glistening appearance by the strands of pink-tan fibrin.

☐Microscopically, the pericardial surface here shows strands of pink fibrin extending outward. There is underlying inflammation. Eventually, the fibrin can be organized and cleared, though sometimes adhesions may remain

☐The combination of endo- and myocarditis is referred to as rheumatic carditis,
☐and that of endo-, myo- and pericarditis – as rheumatic pancarditis.
Vasculitis
☐in rheumatism has systemic nature and is observed in all organs and tissues.
☐Capillary permeability increases drastically, it manifests itself clinically in nodular erythema.
☐It often occurs that skin capillaries are wrapped in pericyte muffs and endothelium is in the state of proliferation. In the end there develops sclerosis around capillaries with the formation of rheumatic nodes.

☐Polyarthritis is usually serofibrinous in rheumatism.
☐ Articular cartilage is not damaged so there can be no articular deformation.

☐Juvenile chorea is a cerebral form of rheumatism. It occurs more often in children.
☐Because of vasculitis there develop dystrophic changes of nerve cells in the brain as well as destruction focuses and haemorrhages that are the morphologic basis of clinical presentations.

☐Rheumatism complications are connected in most cases with heart lesion:
☐valvular defects and
☐emboliSms in verrucous endocarditis, internal infarcts,
☐ encephalomalacia,
☐limb gangrene,
☐ commissures and obliteration of pericardial cavity.
☐The most frequent cause of death of rheumatism is *decompensated valvular defect* and
☐ *thromboembolic complications*.
decompensated valvular defect

Rheumatoid arthritis

☐is a chronic disease based on *progressive disorganization* of *connective tissue* of synovial membranes and *articular cartilages*.
☐Its characteristic feature is the development of nonsuppurative proliferative synovitis followed by *articular deformations*.

Rheumatoid arthritis

☐often causes damage to skin,
☐ blood vessels,
☐ heart,
☐lungs,
☐muscles and
☐ other organs and tissues.
☐It affects mainly women.

☐The cause of the disease is unknown but one points out genetic susceptibility to autoimmune reactions to collagen of Type2. T-lymphocytes release inflammatory mediators and lytic cytokines that destroy joints.
☐ Microbial infection, especially viruses, is often the starting point for the disease.
☐The body produces antibodies to its own Ig G, which is the rheumatoid factor.

☐Morphologic changes mainly manifest themselves in the lesion of musculoskeletal system.
☐synovitis develops of three stages
The first stage
☐is characterized by edema of synovial membrane with the development of disorganization of connective tissue: mucoid and fibrinoid swelling, fibrinoid necrosis. The villi necrotize and there develops “rice body”. There are signs of inflammatory reaction of cells in tissues

☐This is the synovium in rheumatoid arthritis. There is chronic inflammation with lymphocytes and plasma cells that produce the blue areas beneath the nodular proliferations. This "pannus" is destructive and produces erosion of the articular cartilage, eventually destroying the joint.
The second stage
☐manifests itself in the growth of villi and proliferation of synoviocytes,
☐ in inflammatory cellular infiltration,
☐in the formation of granulation tissue on the joint surface,
☐erosions in articular cartilage,
☐exposure of bone and epiphyses, in osteoporosis.
☐The granulation tissue narrows the joint space, decreases articular mobility and causes luxations and subluxations
The third stage
☐manifests itself in fibrous and bony anchylosis and develops after long progression of the disease. It is defined by complete articular immobility, the formation of rheumatoid nodes around joints with signs of destructive changes in connective tissue.

☐The prominent ulnar deviation of the hands and "swan neck" deformity of the fingers seen here is due to rheumatoid arthritis (RA). This autoimmune disease leads to synovial proliferation with inflammation and joint destruction, typically in a symmetrical pattern involving small joints of hands and feet, followed by wrists, ankles, elbows, and knees. Rheumatoid factor can be identified serologically in most, but not all, RA patients.

☐The main visceral manifestations of rheumatoid arthritis are polyserositis, vasculitis in lungs and heart with disorganization of connective tissue and inflammatory cellular infiltration with lymphocytes, plasmocytes and histiocytes.
☐The heart may be affected by endocarditis with the development of valvular disease, the lungs – by pneumosclerosis.

☐Sometimes persons with rheumatoid arthritis (RA) have rheumatoid nodules form in subcutaneous locations at pressure points, such as the elbow shown here. Rheumatoid nodules may also appear viscerally, such as on the pleura of the lung.

☐Here is a rheumatoid nodule. Such nodules are seen in patients with severe rheumatoid arthritis and appear beneath the skin over bony prominences such as the elbow. They can occasionally appear in visceral organs. There is a central area of fibrinoid necrosis surrounded by pallisading epithelioid macrophages. and other mononuclear cells.

☐One of the complications is renal *amyloidosis* with the development of uraemia which is often the cause of patient's death.

Bechterew's (Strumpell's) disease (poker back)

☐or anchylosing spondylitis, rheumatoid spondylitis is a chronic rheumatic disease characterized by the lesion of articular-and-ligamentous apparatus of spine that ends with its immobility.

☐ In its *aetiology* and *pathogenesis* the main role is played by infectious and allergic factors, spinal trauma and heredity.
☐ More often it affects men
The pathologic anatomy
☐is characterized by the development of destructive-inflammatory changes in the tissues of small spinal joints with the destruction of articular cartilage and the development of bony anchylosis. Similar transformations develop in intervertebral disks. The spine becomes completely immobile.

☐It also damages internal organs: aorta,
☐ heart,
☐lungs.
☐There develops renal amyloidosis which is often the cause of death.

Systemic lupus erythematosus (SLE) (Libman-Sacks disease)

☐is a systemic disease marked by autoimmunization that has acute or chronic progression and is characterized by the lesion of skin, vessels and kidneys.
☐ More often it affects young women.

☐*The cause* of the disease is unknown.
☐A nonspecific provoking factor is ultraviolet radiation and pregnancy. The disease may develop after a viral infection.
☐Hereditary factors play an important role too.

☐In its *pathogenesis* a significant role is played by the imbalance of the function of T-suppressors and T-helpers with the formation of multiple organ antibodies (lupous factor – antinuclear antibodies).
The *pathologic anatomy*
☐is characterized by the development of fibrinoid changes in the walls of microcirculation vessels with the formation of vasculitis that ends with secondary ischemic changes in organs in the form of dystrophy and necrosis.

☐*Skin* is affected by cheek erythema – "red butterfly" – due to proliferative-destructive vasculitis in the derma; edema and focal perivascular lymphohistiocytic infiltration.

Kidneys

☐are affected by lupous glomerulonephritis or mesangioproliferative glomerulonephritis. A characteristic peculiarity is the deposition of immune complexes and capillary thickening in the form of "wire loops", fibrinoid necrosis focuses, hematoxylin bodies, hyaline thrombi.

☐Glomerulonephritis results in contraction of kidneys and the development of renal insufficiency which is often the cause of patient's death.

heart

☐is affected by nonbacterial verrucous Libman-Sacks endocarditis where hematoxylin bodies can be found in the necrosis focuses.

☐ In contrast to rheumatism no mucoid or fibrinoid intumescence can be observed.

Libman-Sacks endocarditis

☐Here are flat, pale tan, spreading vegetations over the mitral valve surface and even on the chordae tendineae. Thus, these vegetations that can be on any valve or even on endocardial surfaces are consistent with. These vegetations appear in about 4% of SLE patients and rarely cause problems because they are not large and rarely embolize. Note also the thickened, shortened, and fused chordae tendineae that represent remote rheumatic heart disease.

☐In spleen one can find periarterial "bulbous sclerosis".

☐Among complications and causes of death of SLE one should highlight lupous nephritis and the development of renal insufficiency.

Systemic scleroderma (systemic sclerosis)

☐is defined by the development of diffuse sclerosis and

☐hyalinosis of connective tissue in various organs and tissues.

☐The *aetiology* and *pathogenesis* is unknown.

☐Important to the disease development are viral infections and

☐hereditary factors with

☐autoimmunization.

Pathologic anatomy

☐ Major changes develop in:

☐the heart,

☐kidneys,

☐gastrointestinal tract,

☐blood vessels and

☐ skin.

In the *heart*

☐one can observe sclerosis and contraction of mitral valve cusps, subendocardial cardiosclerosis with the development of cardiovascular collapse – "sclerodermic heart".

☐In coronary vessels one can often find concentric sclerosis and hyalinosis.

☐ Around vessels there is inflammatory infiltration with lymphocytes, macrophages and plasmatic cells.

Skin

☐is affected by diffuse or focal epidermal atrophy,

☐sclerotic transformations and hyalinosis of connective tissue.

☐In dermal vessels one can observe vasculitis and later reduction of bloodstream.

☐Due to insufficient vascularization there appears necrosis and exulceration focuses in the skin.

☐The latter becomes dense, with focuses of hyperpigmentation and hemangiectasia.

□ The face becomes masklike.
In *kidneys*
□there develops progressive vasculitis,
□ concentric thickening of interlobular arteries,
□their trombosis,
□cortical necroses and
□ infarcts, parenchyma
□sclerosis with the development of renal insufficiency.
In *lungs*
□one can observe carnification due to diffuse fibrosis,
□thickening of alveolar septa,
□ arteriolar sclerosis.
In *gastrointestinal tract*
□one can observe sclerotic transformations of submucous and muscular layer,
□swallowing and absorption derangement,
□slowing-down of motility,
□development of cachexy.

Dermatomyositis
□is characterized by the lesion of transversely striated muscles and less by that of non-striated muscles.
□More often it affects skeletal,
□ pharyngeal,
□ laryngeal,
□ ocular and
□ diaphragmatic muscles.

□Muscles undergo atrophic and
□dystrophic changes,
□lose their striation,
□their fermentative activity and glycogen supplies decrease,
□sometimes coagulation necrosis occurs.
□Muscles are gradually substituted by connective tissue and fat masses.

In the heart
□one can observe dystrophy of cardiomyocytes,
□intermediate myocarditis with productive vasculitis,
□ edema of intercellular substance,
□ infiltration with lymphocytes, macrophages and plasmatic cells.
□The process ends with diffuse cardiosclerosis and
□ atrophy of cardiomyocytes.

□In **lungs** alveolar septa are thickened.
□In **gastrointestinal tract** one can observe atrophic and dystrophic transformations of muscular cells, perivascular lymphomacrophage infiltrations, sclerosis of mucous and submucous layer.
□**Other organs** undergo inflammatory and sclerotic changes.
Cardiomyopathies
Dilated (Congestive)

☐ All four chambers are dilated, and there is also hypertrophy. The most common cause is chronic alcoholism, though some may be the end-stage of remote viral myocarditis.

"idiopathic dilated cardiomyopathy")
☐Here is a large, dilated left ventricle typical of a dilated, or congestive, cardiomyopathy. Many of these have no known etiology
☐ while others may be associated with chronic alcoholism. The heart is very enlarged and flabby

☐**Hypertrophic**
☐The most common form, idiopathic hypertrophic subaortic stenosis (IHSS) results from asymmetric interventricular septal hypertrophy, resulting in left ventricular outflow obstruction.
hypertrophic cardiomyopathy
☐There is marked left ventricular hypertrophy, with asymmetric bulging of a very large interventricular septum into the left ventricular chamber.

Restrictive
☐The myocardium is infiltrated with a material that results in impaired ventricular filling. The most common causes are amyloidosis and hemochromatosis.

☐This section of myocardium demonstrates amorphous deposits of pale pink material between myocardial fibers. This is characteristic for amyloid. Amyloidosis is a cause for "infiltrative" or "restrictive" cardiomyopathy
a cardiomyopathy.
☐This very large heart has a globoid shape because all of the chambers are dilated. It felt very flabby, and the myocardium was poorly contractile. This term is used to denote conditions in which the myocardium functions poorly and the heart is large and dilated, but there is no specific histologic finding.

☐Microscopically, the heart in cardiomyopathy demonstrates hypertrophy of myocardial fibers (which also have prominent dark nuclei) along with interstitial fibrosis