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Morphology of autoimmune diseases

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INTRODUCTION

Autoimmune diseases represent complex problem, with growing number of disorders reported, in whose research all aspects of modern immunology are involved. It is known that immune system, under normal circumstances, does not react with self-antigens. This phenomenon (nowadays termed self-tolerance) is first described by Ehrlich (1900) and represents central dogma of modern immunology (1). Self-tolerance is actually essential for individual's ability to live in harmony with his own cells. Comparing to computer logic, where all operations are based on "yes" or "no" differentiation, and electronics where functions are based on "+" or "-" differentiation, immune system function is elementary based on differentiation of "self" and "non-self". Autoimmunity is, therefore, described as a condition in which innate tolerance (areactivity to self) is damaged. As a result of the mentioned, antibodies and immune system cells react with self-antigens causing disease. It should be emphasized here that not all forms of "autoimmune reactions" are "bad" (for example, physiologic reaction with major histocompatibility complex - MHC, necessary for normal immune response). Broad spectrum of autoimmune diseases can be divided to two major groups: systemic (organ-nonspecific) and organ-specific. Certain types of autoimmune diseases may be present together with others, especially in cases of autoimmune endocrinopathies. Typical "representative" of organ-specific autoimmune disorder is systemic lupus erythematosus, marked by autoimmune reactions with self-antigens that are present in more organs. Organ-specific autoimmune diseases are characterized by immune reactions against antigens usually specific for single organ (2). Most frequent systemic autoimmune diseases are: SLE, rheumatoid arthritis (RA), systemic sclerosis (scleroderma), inflammatory myopathies (polymyositis and dermatomyositis), Sjˆgren's syndrome, mixed connective tissue disease (MCTD), systemic vasculites (polyarteritis nodosa and other vasculites), and most common organ-specific autoimmune disorders are represented by Autoimmune thyroiditis (Hashimoto), primary billiary cirrhosis (PBC), autoimmune hepatitis, gastrointestinal disorders (atrophic gastritis, ulcerous collitis, morbus Crohn), skin diseases (pemphigus vulgaris, pemphigus follaceus, bullous pemphigoid).

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Systemic lupus erythematosus - SLE

Morphological changes typical for systemic lupus erythematosus (SLE) are present in almost every organ. Nevertheless, analyses of skin and kidney lesions are of major importance for histopathological diagnosis of SLE. Less important lesions include changes that are present on serous surfaces, joints, cardiovascular system, central nervous system, lungs etc (3,4,5). Skin lesions in SLE are characterized by following changes: hyperkeratosis and parakeratosis, atrophy of Malpighi's layer, liquefactive degeneration of basal epidermal layer, acute necrotizing vasculitis with lymphocytic perivascular and periadnexal islet-like infiltration, connective tissue edema, vasodilatation and extravasation of erythrocytes (6).

2002 WHO/ISN/RPS Classification of Lupus Glomerulonephritis

Class I - Minimal mesangial lupus glomerulonephritis (LGN)
Normal glomeruli by LM, but mesangial immune deposits by IF and/or EM.

Class II - Mesangial proliferative LGN
Purely mesangial hypercellularity of any degree and/or mesangial matrix expansion by LM with immune deposits, predominantly mesangial with none or few isolated subepithelial and/or subendothelial deposits by IF and/or EM not visible by LM.

Class III - Focal LGN (involving less than 50% of the total number glomeruli)
Active or inactive focal, segmental and/or global endo- and/or extracapillary GN, typically with focal, subendothelial immune deposits, with or without focal or diffuse mesangial alterations.

III (A) Purely active lesions: active focal proliferative GN
III (A/C) Active and chronic lesions: active and sclerotic focal proliferative GN
III (C) Chronic and inactive with glomerular scars: active sclerotic focal GN

(indicate the proportion of glomeruli with active and with sclerotic lesions)
(indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents)

Class IV - Diffuse segmental (IV-S) or global (IV-G) LGN
(involving 50% or more of the total number of glomeruli either segmentally or globally)
Active or inactive diffuse, segmental or global endo- and/or extracapillary GN with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) when > 50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) when > 50% of the involved glomeruli have global lesions

IV (A) Active lesions: diffuse segmental or global proliferative LGN
IV (A/C) Active and chronic lesions: diffuse segmental or global proliferative and scleroticLGN
IV (C) Inactive with glomerular scars: diffuse segmental or global sclerotic LGN

(indicate the proportion of glomeruli with active and with sclerotic lesions)
(indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents)

Class V - Membranous LGN
Numerous global or segmental subepithelial immune deposits or their mor-

phologic sequelae by LM and/or IF and/or EM with or without mesangial alterations
(May occur in combination with III or IV in which case both will be diagnosed)

Class VI - Advanced sclerotic LGN
> 90% glomeruli globally sclerosed without residual activity
Kidney is organ widely affected in SLE, and almost all cases of SLE show some renal abnormality. This broad spectrum of kidney lesions, that may be present in SLE but are all non-specific, is marked as Lupus Nephritis and morphologically classified by WHO (2002) to six patterns:
Having on mind this classification, it is of high importance to determine index of activity and chronicity, which may be crucial for diagnosis and can provide better treatment and prognosis of the disease (7-9). Light microscopy analysis, histochemistry, immunofluorescent analysis and electron microscopy analysis have all to be undertaken in order to establish correct diagnosis of kidney disease (Table 1) (10-12).

Table 1. Activity and chronicity index in lupus nephritis

Activity index (0-24)		Chronicity index (0-12)	
Endocapillary hypercellularity	0-3	Sclerotic glomeruli	0-3
Leukocyte infiltration	0-3	Fibrinous crescents	0-3
Subendotehlial hyaline deposits	0-3	Tubular atrophy	0-3
Fibrinoid necrosis/karyorexis	(0-3)x2	Interstitial fibrosis	0-3
Cellular crescents	0-3		
Interstitial inflammation	0-3		

Synovial changes in SLE are manifested by nodular synovitis with hyperplastic synoviocytes and fibrinoid necrosis on synovial surface. Next to synovial tissue lymphocytic proliferation there is large number of plasma cells with Russell bodies (13,14).

Rheumatoid arthritis
Rheumatoid arthritis is chronic inflammatory disease that affects multiple tissues and organs (skin, blood vessels, heart, lungs and muscles). Most prominent changes are present in joints, where non-supurative proliferative synovitis often leads to destruction of cartilage and ankylosis (13,15).
Synovial histopathological changes are represented by following patterns: hypertrophy of synovial cells and subsynovial connective tissue which leads to papillar synovial tissue proliferation; synovial membrane lymphocytic and plasmocytic infiltration (plasmocytes often contain eosinophylic inclusions with gamma-globulin - Russell bodies); lymphoid follicle and germ center formation within synovial tissue; fibrinoid necrosis within or on surface of synovial tissue.
Rheumatoid nodules are most common skin manifestations found in rheumatoid arthritis, and are present in approx. 25% of patients (more likely with ones with more severe course of the disease). Characteristic rheumatoid nodules contain central zone of necrosis surrounded by proliferated connective tissue with radial architecture of cells. Zone of central necrosis contains fibrinoid deposits. Histyocytes are surrounded by large number of lymphocytes, and occasionally plasmocytes (13,16).

Progressive systemic sclerosis (Scleroderma)
This disease is characterized by progressive tissue fibrosis that affects mostly all tissues and organs. Skin is most commonly affected, although gastrointestinal tract, kidneys, heart, muscles, lungs, blood vessels and nervous tissue also undergo pathological changes.
Skin lesions are mostly manifested by edema and perivascular CD 4+ and CD8+ lymphocytic infiltrations, and also by swelling and degenerative changes of collagen fibers that become more eosinophylic. Dermal capillaries and smaller arteries develop thickening of basal lamina, endothelial cell damage and partial occlusion. Following progression of the disease, edema is being replaced by progressive dermal fibrosis. There is prominent dermal connective tissue thickening characterized by presence of hypertrophy, eosinophilic and hyalinised bundles of fibrous tissue. In next phase inflammatory infiltrate usually is rarely present, and it can be seen only around small blood vessels. In some blood vessels wall thickening with occlusion may be present. Sebaceous glands are usually not seen. Sweat glands are atrophic and reduced in number, most commonly surrounded by sclerotic collagen dermal fibers. The fact that sweat glands are placed deeply within dermis (instead of being located at dermo-epidermal junction) speaks in favor of thesis that dermal thickening is caused not only by collagen fibers hypertrophy, but also by synthesis of new collagen in lower derma. Epidermo-dermal junction is not clear. Focal or diffuse calcification might be present in subcutaneous tissue.
There is prominent fibrosis in submucosa and muscularis of esophagus and gastrointestinal tract.
Lungs are affected in more than 53% of the patients. Alveolar walls are thick, may rupture and create cyst-like cavital structures. Diffuse interstitial and alveolar fibrosis with thickening of pulmonary blood vessel walls are histological patterns most often seen in this disease.
Pathological changes may be present in the heart, leading to diffuse myocardial fibrosis with coronary artery disease. Pericardium is usually thick with effusions present on the surface (6,13,17).

Sjögren's syndrome
Sjögren's syndrome is clinicopathological entity characterized by decreased secretion of tears and saliva caused by inflammation of lacrimal and salivar glands. Although those two glands undergo major pathological changes, there are other eccrine glands also affected in this disease (respiratory and gastrointestinal glands, as well as vaginal glands).
Periductal and perivascular lymphocytic infiltration in almost all salivary glands are usually earliest histopathological findings in this disease. Lymphocytic infiltration may be very prominent in large salivary glands and lead to creation of lymphatic follicles with germinative centers. Canalicular epithelium may be hyperplastic and cause narrowing of canalicular lumen. Old changes are commonly manifested by atrophy, fibrosis and hyalinisation of the gland leading to adipous replacement of glandular tissue. In some cases lymphocytic infiltration may be vary prominent and similar to the one seen in lymphoma. Benign lymphocytic pattern, heterogeneous cell population and well-preserved lobular architecture of the gland, though, are parameters that are of major assistance in differentiation of this lesion from lymphoma (13,18-20).

Dermatomyositis and polymiositis
The terms dermatomyositis (dermatopolymyositis, DPM) and polymyositis are related to inflammatory autoimmune myopathies that can be expressed in almost any age, solitary or associated with other disease.
DPM is a rare autoimmune disease manifested by skin and muscle tissue inflammation. Histopathological analysis of muscle tissue in early stage of the disease reveals degenerative myofibril changes of various intensity degree like loss of cross-striation, fragmentation and swelling. Sarcoplasma becomes homogenous, more eosinophilic and with signs of vacuolar degeneration. Lymphocytes and macrophages often surround and destroy myofibrils, leading to loss of sarcolemma and finally sarcolysis. Myofibrilar necrosis is usually segmental and does not affect whole fiber at once. Morphological changes of various degree are present in muscle tissue. One power field may show loss of cross-striation, other may show complete necrosis of myofibrils. Necrosis of single myofiber is more commonly seen in polymyositis than in dermatomyositis and is important parameter in establishing activity index of the disease. Fibrous and adipous tissue replace necrotized myofibrils. The process is followed by myofibrilar regeneration, whose cytoplasm is basophilic, nuclei are large, peripherally or centrally placed and have large nucleoli.
Polymyositis is characterized by following histolopatholgical finding: focal and endomysial inflammatory infiltrate predominantly consisted of lymphocytes

and macrophages, and rarely present perivascular infiltrate. Inflammatory infiltrate is typically placed around damaged myofibrils. Myofibrilar degeneration and necrosis may be present without inflammatory infiltration. Single myofirbil necrosis is frequently found in polymyositis, and inflammatory cells usually affected both narcotized and undamaged myofibrils (13,21-23).
Autoimmune diseases described in this text are the ones most frequently diagnosed by pathologist. There is also growing pool of other autoimmune disorders where histopathological finding from tissue biopsy or autopsy may play crucial role in establishing the final diagnosis of the disease.

REFERENCES

1. Ehrlich P. Gesammelte Arbeiten zur Immunit‰tsforchung. Berlin: Hilschwald; 1904.

2. Theofilopoulos AN. Autoimmunity. In: Stites DP, Stobo JD, Wells JV, editors. Basic & Clinical Immunology. New York: Appleton &Lange; 1987. p. 126-57.

3. Petrović R. Sistemski eritemski lupus. In: Pilipovic N, editor. Reumatologija Beograd: Zavod za udžbenike i nastavna sredstva; 2000. p. 384-7.

4. Tatić V, Dimitrijević J, Mitrović D, Popović M. Značaj histopatoloških ispitivanja u dijagnozi reumatičnih bolesti. In: Popović M, editor. Reumatične i slične bolesti. Beograd: Vojno-izdavački zavod; 2000. p. 842-56.

5. American College of Reumathology ad hoc, Committee on systemic lupus erythematosus in adults. Artritis Rheum 1999;42:1785-96.

6. Barnhill RL. Textbook of Dermatopathology. Mc Graw-Hill; 1998.

7. Hill GS. Toward a new classification of lupus nephritis. Short course 9 "Glomerular disease". International Academy of Pathology 2002; October 5-10; Amsterdam, Holland; 32002. p. 2-5.

8. Ponticelli C, Maroni G. Renal biopsy in lupus nephritis-what for, when and how often. Nephrol Dial Transplant 1998;13:2452-4.

9. Dimitrijević J, Đukanović Lj, Kovačević Z, Bogdanović R, Maksić Đ, Hrvačević R et al. Lupus nephritis: histopathological features, classification and histologic scoring in renal biopsy. Vojnosanit Pregl 2002;59 6 Suppl:21-31.

10. Churg J, Bernstein J, Glassock RJ. Renal Disease. Classification and Atlas of glomerular diseases. New York: Igaku Shoin; 1995.

11. DimitrijevićJ, Spasić P, Marić M, Kovačević Z, Hrvačević R, Maksić D et al. Znacaj biopsija bubrega u dijagnostici glomerulonefritisa. Medicinski časopis UDC 61 1995;34:29-42.

12. Bogdanović R, Nikolić V, Pašić S, Dimitrijević J, Lipkovska-Marković J, Erić-Marinković J et al. Lupus nephritis in childhood: a review of 53 patients followed at a single center. Pediatr Nephrol 2004;19:36-44.

13. Robbins SL. Pathologic basis of disease. Philadelphia: W.B.Saunders Company; 1994.

14. Chou C, Schumacher HR. Clinical and pathological studies of synovitis in polymyalgia rheumatica. Arthritis Rheum 1984;27:1107-17.

15. Peltonen L, Puranen J, Hamalainen M, Kalevi KL. Histopathological findings in joint diseases. Scand J Rheumathol 1981;10:115-23.

16. Anthony PP, Macsween RNM. Recent Advances of Histopathology. New York: Churchill Livingstone; 1987.

17. Le Roy EC, Black C, Fleishmyuer R, Jablonska S, Krieg T, Medsger TA. Jr Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202-5.

18. Stefanović D, Mitrović D, Popović M. Savremeno shvatanje primarnog Sjogrenovog sindroma. Vojnosanitet Pregl 1991;48:334-7.

19. Stefanović D. Klinički značaj imunoloških poremećaja u primarnom Sjogrenovom sindromu (disertacija). Beograd: VMA; 1993.

20. Bloch JK, Buchanan WW, Wohl MJ. Sjogren`s syndrome. A clinical pathological and serological study of sixtu two cases. Medicine1965;44:187-231.

21. Bohan A, Peter JB. Polymiositis and dermatomyositis (first of two parts). N Engl J Med 1975; 292:334-7.

22. Tanimoto K, Nakano K, Kano S et al. Classification criteria for polymyositis and dermatomyositis (seecomments) published erratum apears in J Rheumatol 1995;22:668-74.

23. Petrović-Rackov LJ, Mitrović D, Anđelković Z, Popović M. Dermatopolimiozitis u overlap sindromima. Vojnosanit Pregl 1998;55:27-32.