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THE MORPHOGENESIS AND THANATOGENESIS OF THE POLY-ORGANIAL LESIONS IN FAMILIAL MEDITERRANEAN FEVER

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Abstract

Familial Mediterranean fever (FMF) or periodic disease (PD) is known as a widespread disease in Armenia and countries surrounding the Mediterranean basin. The FMF is characterized by recurrent fever, peritonitis, pleuritis, pericarditis, skin lesions, arthritis, it is frequently complicated by systemic amyloidosis with predominantly affection of kidneys leading to death at relatively young age.

Clinical-morphological analysis of 185 patients with FMF and dissection material of 52 persons dead from complications of FMF without renal transplantation was done.

The purpose of the present study is to characterize the clinical and morphological features and organopathological manifestations in patients with FMF and those dead from complications to evaluate tanatogenesial peculiarities of disease. We have observed cardiac amyloidosis manifested with cardiomegaly, thickening of intraventricular septa and left ventricular wall. Microscopically amyloid was distinguished in myocardium intramural vascular walls and in the stroma. Amyloidosis was more expressed in arteriolar walls also, with narrowing or completely closing of vascular lumina. In thanatogenesis progressing left or/and right ventricular insufficiency prevailed in two cases only. Cardiac amyloidosis resulting in heart failure and death in these cases developed before the renal failure. FMF with cardiac involvement was accompanied with ischemic heart disease in 2 cases. Sometimes cardiac amyloidosis was distinguished microscopically, without macroscopical characteristic features and clinical manifestations. The lung amyloidosis in all cases was accompanied with cardiac amyloidosis.

In dissection material nonamyloid nephropathias (intracapilliary or extracapilliary glomerulonephritis) were also observed. In investigated material we classified the kidney affections connected with FMF in 3 groups: kidney amyloidosis, nonamyloid affections and glomerulitis accompanied with amyloidosis in glomerules and vessels. Nonamyloid renal affections in FMF lead to more progressing renal failure and death.

Keywords: Familial Mediterranean fever, amyloidosis, nonamyloid affections, morphogenesis, thanatogenesis.

INTRODUCTION

Familial Mediterranean fever (FMF) or Periodic disease (PD) is a hereditary disorder that manifests with fever and transient polyserosites: peritonitis, pleurisy, pericarditis [*Ayvazyan A., 1982; Pras M., 2002, Yeganyan G.A., 2005, Cakalagaoglu F. et al., 2007*]. The disease, despite its prevalence only in certain ethnic groups, including those from the Mediterranean region, invariably attracts the attention of researchers by peculiarity of the clinical picture, and especially in relation to the incidence of amyloidosis [*Cattan D. et al., 2000; Yildiz A. et al., 2001*].

Amyloidosis refers to the most serious complications of FMF with the prognostic significance [*Ben-Chetrit E., 2003; Erdem H. et al., 2006*]. Renal amyloidosis is the most frequent complication of disease leading to renal failure and death in the majority of patients.

Discovery of the gene MEFV (MEditerranean FeVer) became a confirmation of the hereditary nature of this disease. Currently, at least 29 mutations of the FMF gene have been identified; this became a

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prerequisite for undertaking research on the relationship between genotype and clinical features of manifestations of the disease, including amyloidosis [*Cazeneuve C. et al., 2000; Sarkisian T. et al., 2007; Touitou I. et al., 2007; Amaryan G., 2010*].

Diagnosis of the disease is mainly clinical, with the help of genetic testing and histological biopsy material. The latter is important for detecting amyloidosis [*Halloush R. et al., 2009*].

Investigation of FMF in Armenia is particularly actual, because the incidence in recent decades has increased considerably. In addition, studies concerning morphological features, atypical forms, clinical-morphological correlations of FMF are not numerous.

The investigation was aimed at a study on clinical and morphological features of multiple organ lesions in periodic disease for identification of dominant morphologic lesions in thanatogenesis in parallel with the clinical manifestations, as well as revealing nonamyloid renal affections.

MATERIAL AND METHODS

A clinical and morphological analysis of 185 patients with FMF and 52 sectional observations of those dead from the complications of FMF were done. Operational, operational-biopsy and puncture-biopsy material from patients with FMF was studied, including thyroid, kidney, biopsies from the stomach, duodenum, large (sigmoid and rectum) intestines. The investigated material was classified to the clinical forms and stages of FMF, according to the patient's age and period of manifestation of the disease.

Pieces were taken from various organs, fixed in neutral formalin and then paraffin sections were obtained. Histological preparations were stained with hematoxylin and eosin, methyl violet, Congo red, followed by polarization microscopy, thioflavin T (Sigma Aldrich, Germany).

RESULTS

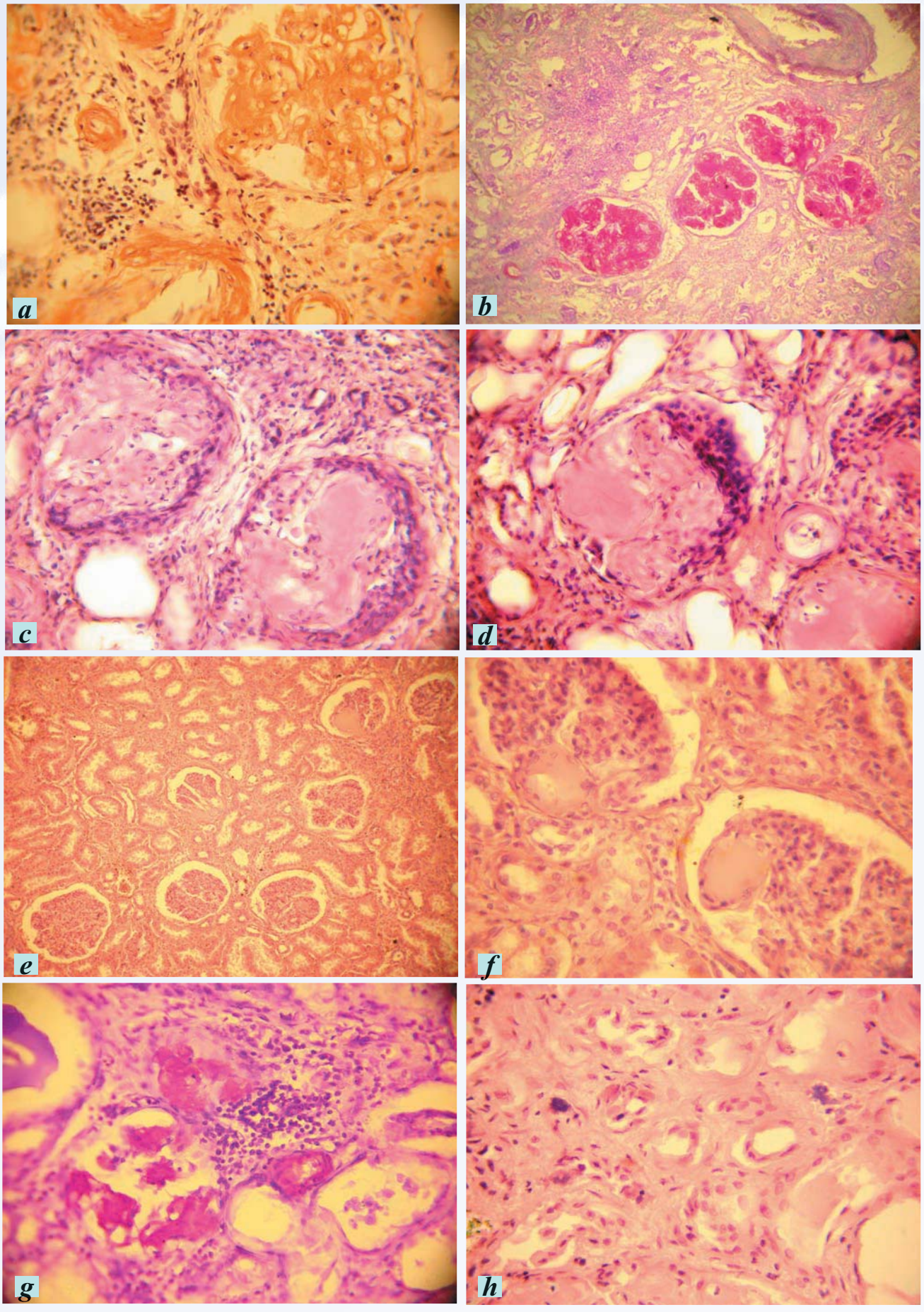
The result of our investigations revealed that the severity of amyloidosis in various cases and the degree of affection of different organs are variable. Amyloidosis in the kidneys, spleen, endocrine organs, digestive organs, except liver, was revealed more often and more sharply. Amyloidosis was weakly expressed in liver, heart, and lungs.

It was established that renal affection was observed in all patients, who died from complications of FMF, but the severity and nature of the observed changes were different. Basically, they manifested as an amyloidosis and glomerulitis. Renal amyloidosis was detected in autopsy and biopsy material with amyloid depositions in the glomerules and vascular walls (Figure 1a; b), and classified according to "Scoring and Grading System" in 6 groups [*Sen S. et al., 2010*]. Glomerular amyloidosis was sometimes accompanied by proliferation of capsular nephrothelium (Figure 1 c; d). The lymphohystiocytic and plasmocytic infiltrations of kidneys stroma were identified (Figure 1g).

In 15.4% cases investigated by us nonamyloid kidney disorders were found. Intracapilliary mesangioproliferative or extracapillary productive glomerulonephritis with proliferation of nephrothelium and podocytes like "crescents" was observed. Sometimes glomerulitis was identified along with lobular amyloid deposits in the glomerular mesangium (Figure 1 f; e). In these cases angiomatosis in the interstitium of kidneys with endothelial cell proliferation was often revealed (Figure 1 h).

In 2 cases the progressive left ventricular heart failure in thanatogenesis prevailed. Macroscopically cardiomegaly, thickening of the heart valves, intra-

Figure 1.
Amyloid deposits in the glomerules, VI class on "Scoring, and Grading System".
- ***a)****. Glomerular and vascular amyloidosis with lymphoid cell accumulations in the stroma, Congo red, x400;*
- ***b)****. glomerular amyloidosis, Methyl violet, x100;*
- ***c)*** *Amyloid deposits in the glomerules with proliferation of capsular nephrothelium, hematoxylin and eosin, x400;*
- ***d)****. Amyloid deposits in the glomerules with severe proliferation of capsular nephrothelium, hematoxylin and eosin, x400;*
- ***e)*** *Mesangioproliferative glomerulonephritis with lobular accumulations of amyloid in the glomerules, with hyaline-droplet dystrophy of tubular epithelium, hematoxylin and eosin, x100;*
- ***f)****. Mesangioproliferative glomerulonephritis with lobular accumulations of amyloid in the glomerules, hematoxylin and eosin, x400;*
- ***g)****. Lymphocytic infiltration of the stroma of the kidney, amyloid accumulations in mesangium of glomerules and in the vascular wall, methyl violet, x400;*
- ***h)****. Angiomatosis of kidneys interstitium with vascular endothelial cell proliferation, hematoxylin and eosin, x100.*



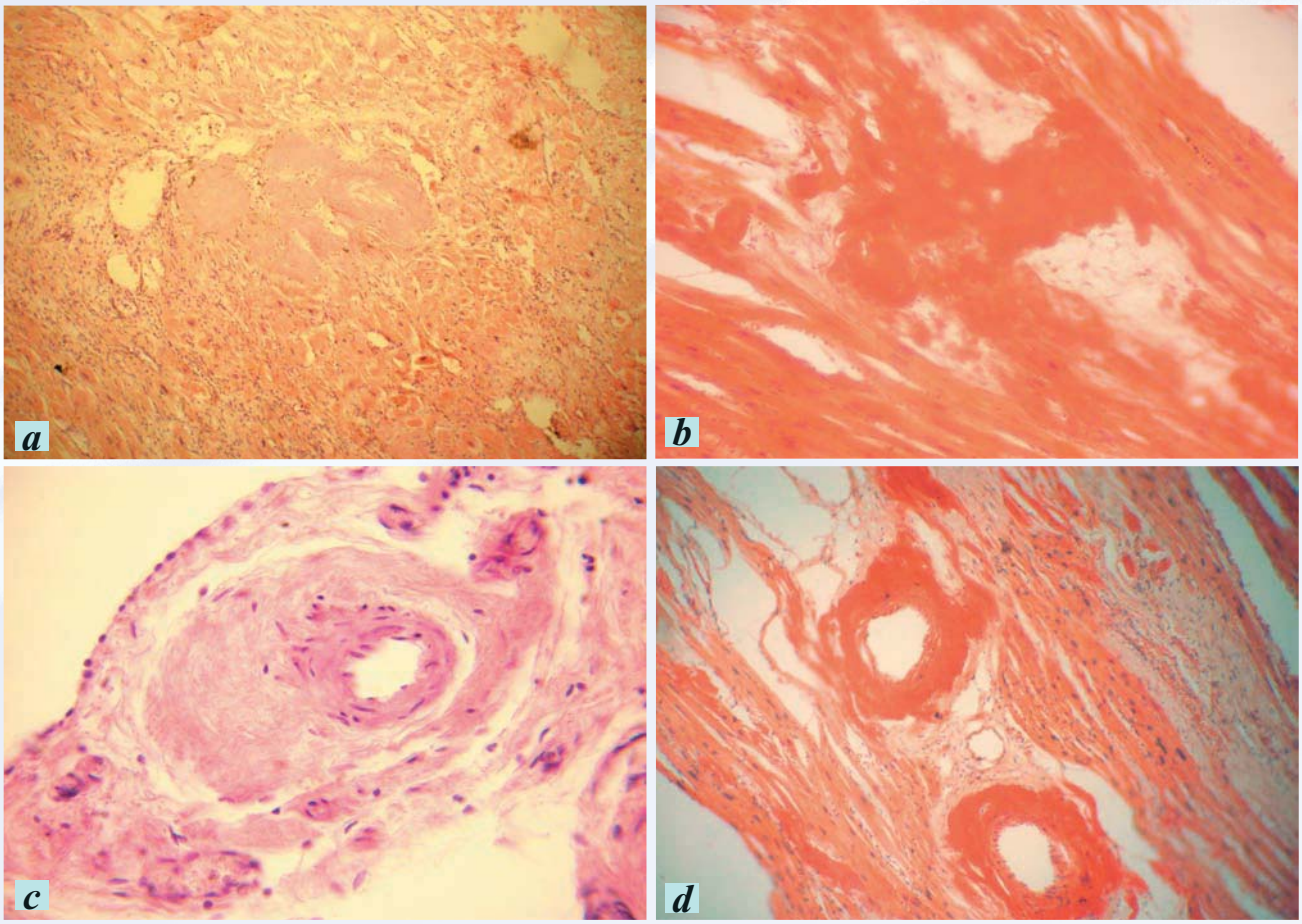


Figure 2. *Cardiac amyloidosis.*
***a)** Amyloid masses in the stroma of the myocardium with hypertrophy of cardiomyocytes, hematoxylin and eosin, x100;*
***b)**. Amyloid masses in the stroma of the myocardium with hypertrophy of cardiomyocytes, Congo red, x200;*
***c)** Periadventitial amyloidosis of small-caliber artery in myocardium, hematoxylin and eosin, x400;*
***d)**. Periadventitial amyloidosis of small-caliber artery in myocardium, Congo red, x200.*

ventricular septa and left ventricular wall were revealed. Amyloid deposits in the endocardium, stroma of the myocardium, as well as in vascular walls of all types were microscopically determined (Figure 2 a; b). Especially large amyloid deposits were detected in small arterial and venous vessels partially in myocardium and epicardium. In a few vessels of larger caliber amyloid deposition was determined in the adventitia and periadventitial tissue (Figure 2 c; d).

In the stroma of myocardium amyloid masses displaced the muscle tissue of the heart, leading to atrophy of cardiomyocytes. Different groups of muscle fibers were hypertrophied. In some areas dystrophic changes of cardiomyocytes were found. Around the amyloid mass diffuse proliferation of connective tissue with perifocal moderate lymphoplasmocytic infiltration was revealed.

It is of interest that in the studied material cardiopathic amyloidosis was diagnosed in cases when nonamyloid kidney affections were frequently detected. In all cases of cardiac amyloidosis it was accompanied by the lung affections. Pulmonary amyloidosis clinically manifested as pneumonia or lung hypertension. In the autopsy material pleural thickening with accumulations of amyloid lumps was revealed. The expressed amyloidosis was revealed in interalveolar septas, the walls of the bronchioles and bronchi, as well as in the stem bronchi and trachea under the *lamina propria* of the mucosa and in the walls of the glands with atrophy (Figure 3 a; b; c; d), in the vascular walls and surrounding the vessels (Figure 3 e; f). Mostly there was desquamation of lining epithelium. In the lung tissue calcifications were revealed. In some cases, areas of fibrosis were found. Clinically, patients showed pulmonary hypertension.

At histological examination, in autopsy, puncture-biopsy, and/or surgery material of thyroid gland masses of amyloid were found in the stroma with

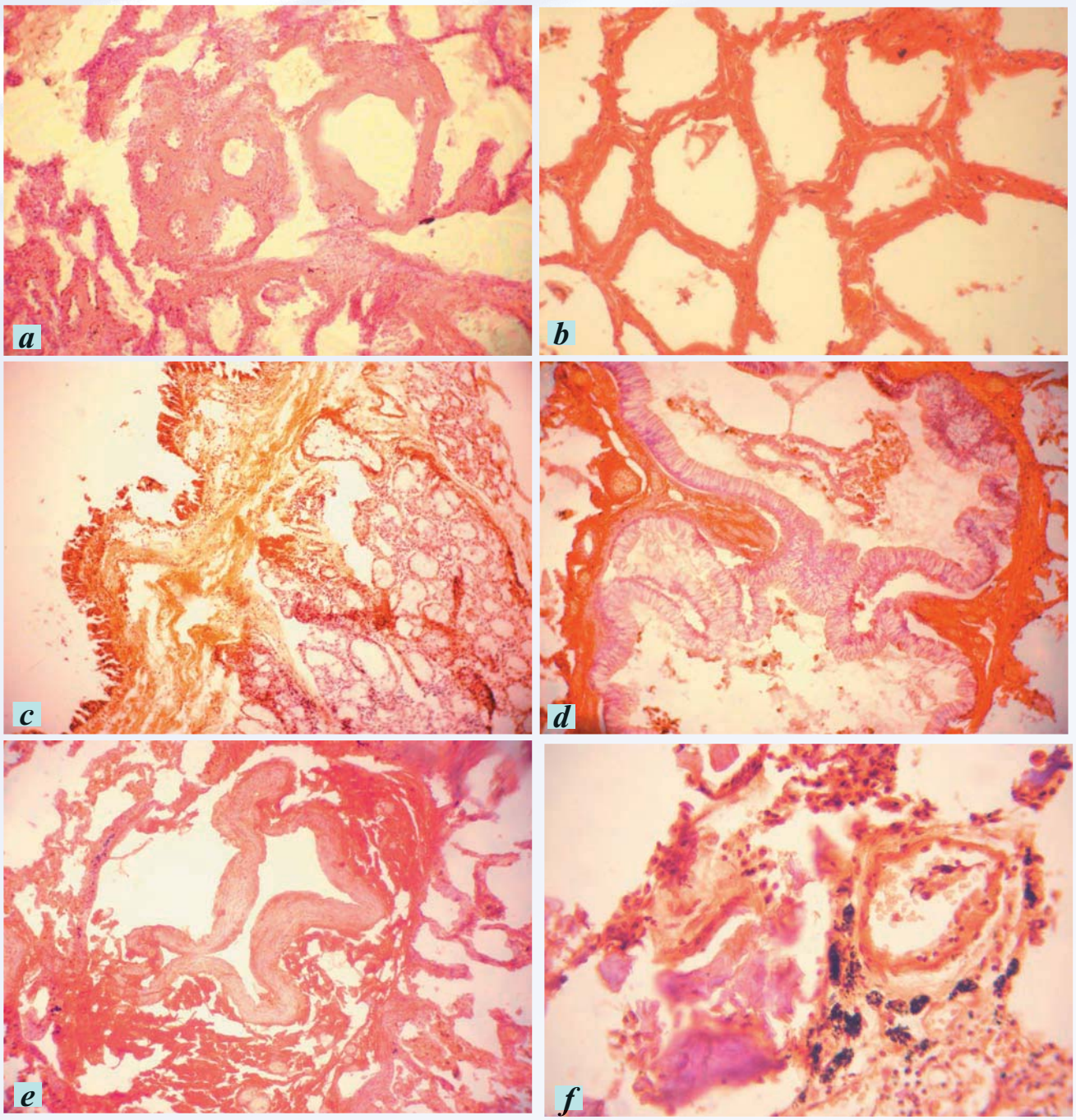


Figure 3. *Amylodosis of the lungs.*
a) *Amyloid deposits in alveolar passages of the lung, hematoxylin and eosin, x400;*
b)*. Amyloid deposits in alveolar passages of the lung, congo red, x200;*
c) *Amyloid depositions in the bronchial wall by the lamina propria of the mucosa and in glands walls; hematoxylin and eosin, x400;*
d) Amyloid depositions in the bronchial wall by the lamina propria of the mucosa and in glands walls, Congo red, x200;
e) Amyloid deposits of the vascular walls and perivascular tissue, Congo red, x200.
f)*. Amyloid deposits of the vascular walls and perivascular tissue, Congo red, x400.*

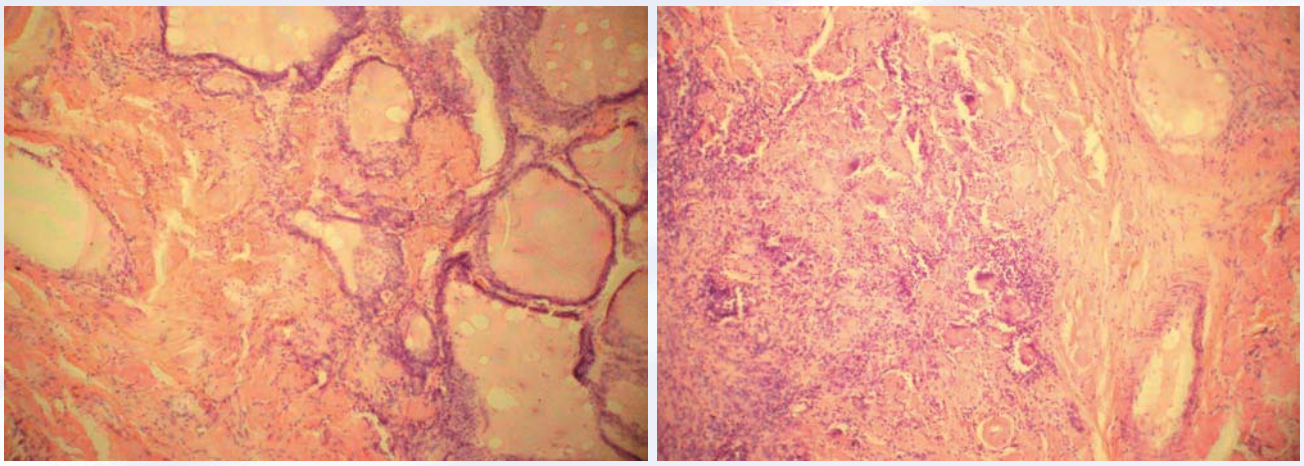


Figure 4. *Thyroid amyloidosis.*
***a)**. Amyloid accumulations in the stroma of thyroid, Congo red, x400;*
***b)**. Lymphoid-cellular and giant-cellular reaction around the amyloid masses in thyroid, Congo red, x400.*

atrophy of the follicles (Figure 4 a). The giant cells surrounding amyloid masses were frequent (Figure 4 b).

The adrenal glands were morphologically investigated in all autopsy cases, and in most cases amyloidosis was revealed. The deposition of amyloid in the cortex, up to complete replacement of stroma with amyloid masses was observed. Amyloid was also determined in medulla: in the vessel walls and around them (Figure 5).

In biopsies from the stomach, duodenum, large intestines, in parallel with the study of autopsy material, amyloid deposits were mainly identified in the small vessels of the arterial type of the mucosal and submucosal membranes (Figure 6). An interesting fact is that the amyloid in these cases was often identified around the adventitia of blood vessels: in peri-adventitial tissue.

In liver amyloidosis is expressed relatively weakly. In the portal fields, in the walls of arteries and arterioles amyloid deposits were revealed, sometimes with considerable thickening of the vascular walls (Figure 7 a; b;). In the intralobular stroma amyloid was rarely detected (Figure 7 c).

In all studied cases amyloidosis of the spleen was revealed: there were 14 cases of sago spleen (Figure 7d) and 27 cases of lardaceous spleen. The markedly expressed amyloidosis and sclerosis of the spleen capsule were revealed.

DISCUSSION

Kidneys are always affected in FMF, but not in all cases renal amyloidosis develops. Sometimes the renal affections are manifested as an intracapilliary mesangioproliferative or extracapillary productive

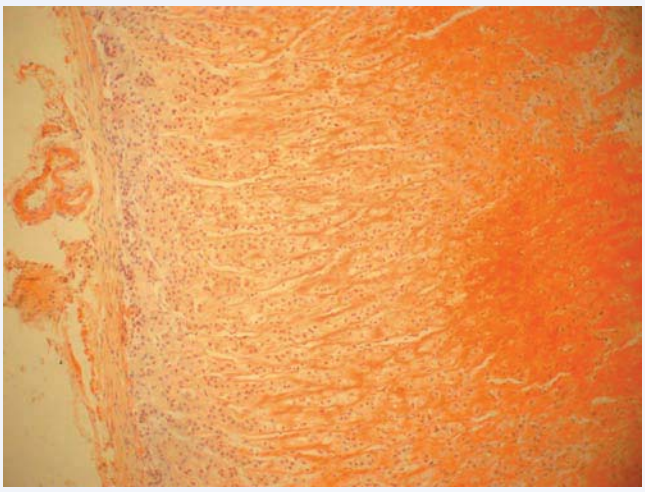


Figure 5. *Amyloid deposits in the stroma of the adrenal gland and in the vessel walls, Congo red, x400.*

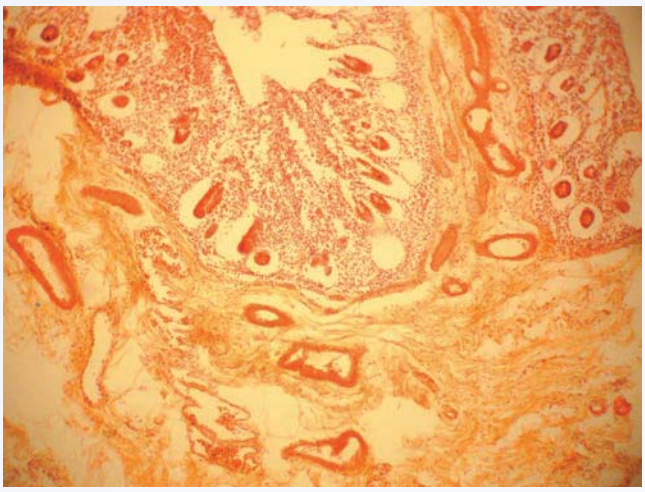


Figure 6. *Amyloid deposits of the vessels in submucosal layer of the small intestine, Congo red, x400.*

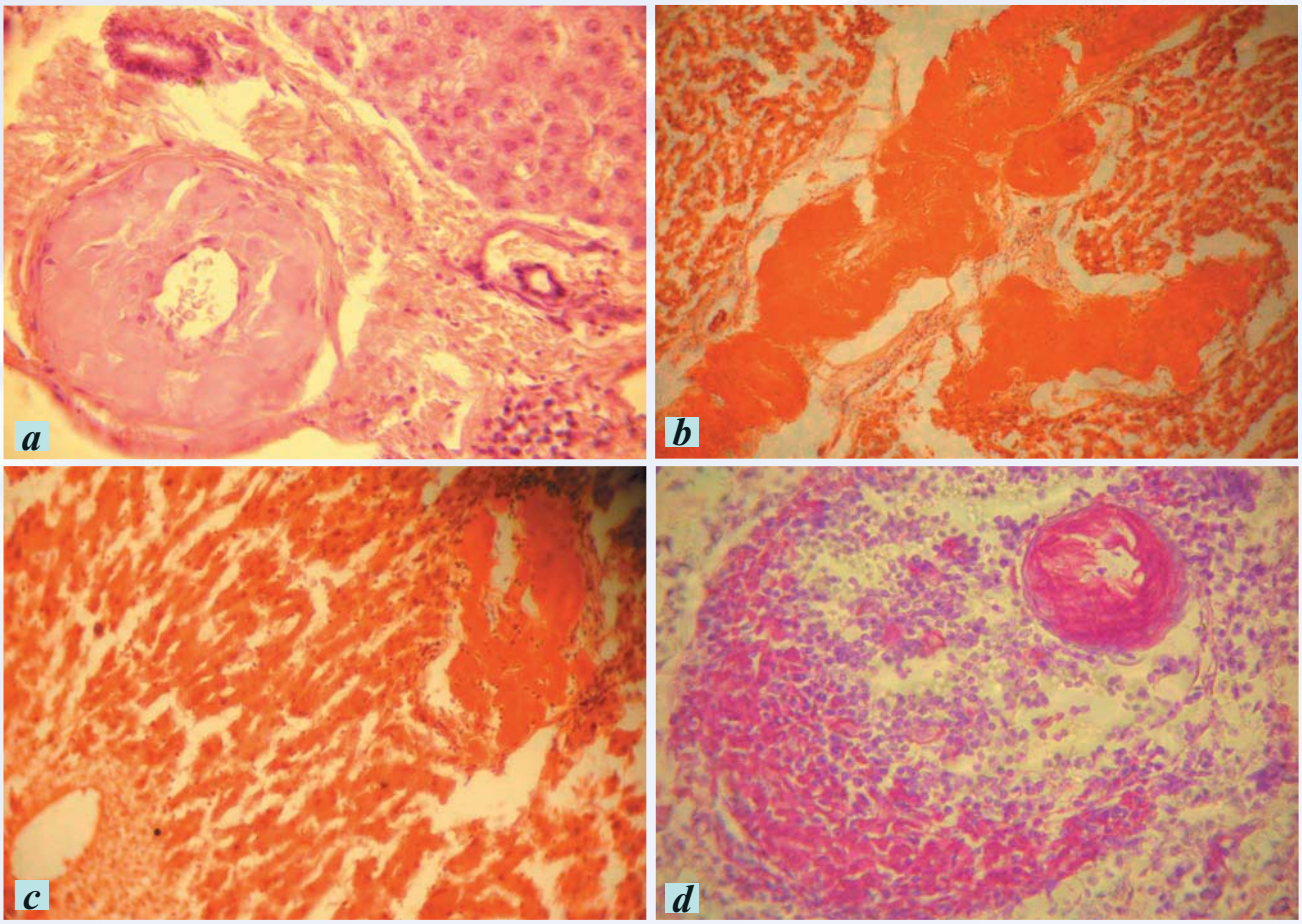


Figure 7. *Liver and spleen amyloidosis.*
***a)**. Amyloid depositions of the arteries in the portal tracts of liver with thickening of the wall, hematoxylin and eosin, x400;*
***b)**. Amyloid masses of the portal tracts of the liver, Congo red, x200;*
***c)**. Amyloid of the liver intralobular stroma, Congo red, x400;*
***d)**. Amyloid depositions in the follicle and the wall of the follicular artery of spleen (sago spleen), methyl violet, x400.*

glomerulonephritis. The latter is often combined with lobular amyloid accumulation in glomerules. According to our research, nonamyloid kidney affections, which give a negative result for amyloid in histological study of puncture-biopsy material, lead to progressive renal failure.

Thus, the observed renal lesions in FMF were attributed to three groups: renal amyloidosis; nonamyloid renal disorders; combined renal amyloidosis and glomerulitis. The last option was identified as amyloid masses of the kidney glomerules with extracapillary productive reaction, and mesangioproliferative glomerulonephritis with lobular accumulations of amyloid in the glomerules.

Cardiopathic amyloidosis, which is known as a lesion atypical for FMF, was identified in cadaver dissection in 4 cases with clinically dominant nephrological and gastrointestinal manifestations of FMF. Only in 2 of these cases we established morphologically dominant cardiopathic amyloidosis leading to death from heart failure. Thus, we evaluated cardiopathic amyloidosis as a clinical and morphological manifestation that is rare, but characteristic for FMF. Pulmonary amyloidosis with delicate amyloid depositions that was frequently identified microscopically, according to our data, proceeds together with the cardiopathic amyloidosis.

According to literature data, at nonamyloid renal lesions amyloid deposits are not detected in other organs [*Ter-Kasparova M., 2002*]. As to investigated material, in the presence of nonamyloid kidney disorders, we detected amyloid deposits in other organs. It is of interest that in such cases we revealed amyloid accumulations in the heart, lungs, liver, adipose tissue, and in other organs not so affected by amyloidosis. Thus, nonamyloid kidney disorders

leading to more progressive renal failure on the one hand, and lesions, which are not diagnosed clinically and aggravate the course of the disease, on the other hand, have a vital role in thanatogenesis of FMF.

Endocrine disorders often proceed clinically latent. Only with advanced cases, there are signs of endocrine insufficiency. Moreover, endocrine amyloidosis (amyloidosis of adrenal glands, thyroid, parathyroid glands, and pancreas) can be clearly manifested morphologically in the autopsy material.

Periadventitial amyloid accumulations of the vessels in myocardium, in gastrointestinal tract submucosa indicate the availability of pericollagenous arranged amyloidosis (alongside with the perireticullary type) in FMF.

The spleen affections are more often and dramatical in FMF. Despite the absence of clinical manifestations, morphologically spleen amyloidosis often dominates.

The nephropathic amyloidosis is not the only dominant manifestation in FMF. There might be cases, when amyloidosis not so typical for FMF (amyloidosis of heart, lungs, adrenal glands, thyroid gland) significantly predominates kidney damage and may be expressed at the forefront of thanatogenesis.

In investigated material, particularly in cases when amyloid is distinctly expressed the presence of lymphohystiocytic infiltrates is typical (Figure 1 a; g). Infiltrates frequently surrounded amyloid degenerated renal glomerules and were detected in the vicinity of massive deposits of amyloid of the kidney, thyroid gland stroma, in the submucosal layer of the small intestine, in small amounts in the stroma of the myocardium. In the thyroid gland, infiltrates also implicated macrophages and giant cells. In the submucosal and muscular layers of the small and large intestines diffuse infiltrates consisting of mainly plasma cells were revealed. The presence of lymphoid-cellular infiltrations in stroma of affected organs indicates the presence of immunological changes in FMF.

As shown by literature data, patients with FMF have a high level of IL-2 in enzyme-immune analysis exceeding the control level 1.6 times. During the FMF attack, γIF level was also high exceeding the control level 2.5 times, while in remission, it is almost exactly the same as in the control group [*Astvatsatryan V. et al., 2003*]. It is known that in the immune system cytotoxic T-lymphocytes, NK-cells and T-helper population of Th-1 are γIF major producers. Based on the foregoing statement, we can assume that there occurs activation of specific T-lymphocyte populations.

Tolerance to amyloid protein fibrils, the expression of which is insufficient and uncomplete amiloidoclasia, might be considered as one of the main reasons for accumulation of amyloid substance in tissues.

Thus, despite the fact that amyloid has a weak immunogenicity, significant changes in the immune status of patients with FMF were observed. Hyperplasia of lymphoid cellular elements and infiltration of kidney tissue surrounding the amyloid-degenerated glomeruli correlated with the immunological changes: the activation of lymphocyte populations and generation of immunocytokines IL-2 and γIF. Production of lymphocyte IL-2 can be stimulated by macrophage IL-1. High level in acute inflammatory attacks of the disease was described in studies of J.P. Drenth [*Drenth J. et al., 2001*].

Generation of IL-1 monocyte/macrophages, which has a central role in inflammation, is stimulated by pyrin [*Gumucio D. et al., 2002; Chae J.,et al., 2006*]. Pyrin, as an inhibitor of caspase-1 and being expressed in neutrophils in acute inflammatory attacks of FMF, itself activates effector cells of the immune response [*Orbach H. et al., 2001; Korkmaz C. et al., 2002; Papin S. et al., 2003*]. Activation of monocytic populations leading to the production of cytokines is accompanied with high levels of plasma protein SAA, as a precursor of amyloid fibrillar protein [*Poland D. et al, 2001*]. The high level of powerful inflammatory immunocytokines IL-1 activates the synthesis of SAA by hepatocytes; from partially degraded products of the latter fibrillar component of amyloid is formed.

As known, the main sources of IL-1 are B-lymphocytic populations and macrophages [*Kulakov V. et al., 1998, Simbirtsev A., 1998*]. However, as the literature data shows, in FMF the level of macrophage IL-1 of children suffering from FMF did not differ from that of the control group [*Astvatsatryan V. et al., 2003*]. In our research the lymphoid cellular stromal infiltrates of the kidneys mainly consisted of lymphocytes, which correlate with published data,

showing high levels of IL-2, therefore we can assume that they relate mainly to the T-lymphocytic population releasing IL-2.

Due to the recent studies it was established that prolactin and IGF-1 act as a powerful motivating factors that provide enhanced synthesis of immunocytokines IL-2 and γIF act [*Matera L., 1996; Yarilin A., 1997; Richards S. et al., 1998*]. It was investigated that the rate of prolactin and IGF-1 regardless from the FMF period exceeded the level of these hormones in the control group. It is not excluded that the synthesis of IL-2 and γIF is due to increased elaboration of prolactin and IGF-1 by adenohypophysis.

Thus, according to histomorphologic study of multiple organ lesions at FMF, amyloid accumulation, the intensity of which correlated with the frequency of acute attacks of disease, as well as with immunological changes, was revealed.

REFERENCES

1. *Amaryan G.G.* [Periodic disease in children: clinical and genetic aspects and modern approaches to treatment] [published in Russian]. Author's Thesis for Doct. Med. Science degree. Yerevan. 2010. 37p.
2. *Astvatsatryan V.A., Zilfyan A.V., Mirzabekyan K.G., Avagyan S.*A.Changes in the content of immunocytokines and pituitary growth hormones in serum of children with periodic disease] [published in Russian]. Medical Science of Armenia. 2003; 4: 53-56.
3. *Ayvazyan A.A*. [Periodic disease] [published in Russian].Yerevan. 1982, 215 p.
4. *Ben-Chetrit E.* Familial Mediterranian fever and renal amyloidosis-phenotype-genotype correlation, treatment and prognosis. J. Nephrol. 2003; 16(3) :431-434.
5. *Cakalagaoglu F., Ikinci A., Koc M., Arıkan H.* Renal amyloidosis-correlation morphology and clinical features. Virchows Arch. 2007. p. 451-515.
6. *Cattan D., Dervichian M., Dode C. et al.* MEFV mutations and phenotype-genotype correlations in north African Jews and Armenians suffering from FMF. In: FMF II International conference, 3-7 May 2000, Antalya - Turkey. Lectures and Abstracts. § 79.
7. *Cazeneuve C., Hyrapetyan H., Papin S., Roudout-Thoraval F. et al*. Identification of MEFV-independent modifying genetic factors for Familial Mediterranian Fever. Am. J. Hum. Genet. 2000; 67: 1136-1143.
8. *Chae J.J., Wood G., Masters S.L., Richard K., Park G., Smith B.J. et al.* The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1beta production. Proc Natl. Acad. Sci. USA. 2006; 103: 9982-9987.
9. *Drenth J.P., Van der Meer J.W., Kushner I.* Hereditary periodic fever. Engl. J. Med. 2001; 345: 1748-1757.
10. *Erdem H., Simsek I., Pay S., Dinc A., Deniz O., Ozcan A*. Diffuse pulmonary amyloidosis that mimics interstitial lung disease in a patient with familial Mediterranean fever. J. Clin. Rheumatol. 2006; 12(1):.34-36.
11. *Gumucio D.L., Diaz A., Schaner P., Richards N., Babcock C., Schaller M. et al*. Fire and ICE: the role of pyrin domain-containing proteins in inflammation and apoptosis. Clin. Exp. Rheumatol. 2002; 20:.45-53.
12. *Halloush R.A., Lavrovskaya E., Mody D.R., Lager D., Troung L*. Diagnosis and typing of systemic amyloidosis: The role of abdominal fat pad fine needle aspiration biopsy. Cyto Journal, 2009, 6: 24.
13. *Korkmaz C., Ozdogan H., Kasapcopur O., Yazici H.* Acute phase response in Familial Mediterranean Fever. Ann. Rheum. Dis. 2002; 61: 79-81.
14. *Kulakov V.V., Simbirtsev A., Kotov A., Chernousov A.D., Pinegin B.V.* [Effect of monoclonal antibodies against interleukin-1 on the cytotoxic properties of human peripheral blood neutrophils] [published in Russian]. Immunology. 1998; 4: 39-40.

15. *Matera L.* Endocrine, paracrine and autocrine actions of prolactin on immune cells. Life Sci. 1996, 1, 8, p. 599-614.

16. *Orbach H., Ben-Chetrit E.* Familial Mediterranean fever. Minerva Med. 2001; 92: 421-430.

17. *Papin S., Cazeneuve C., Duguestony P., Jeru I., Sahai D., Amselem S.* The tumour necrosis factor alpha-dependent activation of the human Mediterranean fever (MEFV) promoter is mediated by a synergistic interaction between C/EBPbeta and NFkB p65. J. Biol. Chem. 2003; 278: 48839-48847.

18. *Poland D.C.W., Drenth J.P.H., Rabinovitz E., Livneh A., Bijzet J., Van Het Hof B., Van Dijk W.* Specific glycosylation of α1-acid glycoprotein characterizes patients with familial Mediterranean fever and obligatory carriers of MEFV. Annals of the rheumatic diseases. 2001; 60(8): 777-780.

19. *Pras M.* FMF: Past, present and future. Clin. and Exper. Rheumatol. 2002; 4 (26): 66.

20. *Richards S.M., Garman R.D., Keyes L., Kavanagh B., McPherson J.M.* Prolactin is an antagonist of IGF-b activity and promotes proliferation of murine B-cell hybridomas. Cell. Immunol. 1998; 184(2): 85-91.

21. *Sarkisian T., Hayrapetyan H., Beglaryan A., Shahsuvaryan G., Yeghiazaryan A.* [Molecular Diagnosis of Familial Mediterranean fever in Armenians. The New Armenian Medical Journal. 2007; 1(1): 33-40.

22. *Sen S., Sarsık B.* A Proposed Histopathologic Classification, Scoring, and Grading System for Renal Amyloidosis: Standardization of Renal Amyloid Biopsy Report. Archives of Pathology & Laboratory Medicine. 2010; 134(4): 532-544.

23. *Simbirtsev A.S.* [Biology of interleukin-1 family of humans] [published in Russian]. Immunology. 1998; 3:.9-16.

24. *Ter-Kasparova M.R.* [Organopathology of periodic disease] [published in Russian]. "Sahak Partev" Publishing House. Yerevan. 2002. 166p.

25. *Touitou I., Sarkisian T., Medlej-Hasim M., Tunca M., Livneh A. et al.* Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. Arthritis & Rheum. 2007; 56 (11): 3879-3880.

26. *Yarilin A.A.* [The system of cytokines and principles of its functioning in norm and pathology] [published in Russian]. Immunology, 1997, 5, pp. 7-13.

27. *Yeganyan G.A.* [The new hypothesis of famlial Mediterranean fever attacks pathogenesis and amyloidosis development][published in Armenian]. Blood, 2005, 1 (1), pp 80-85.

28. *Yildiz A., Akkaya V., Kilicaslan I., Turkmen A., Gorcin B., Atilgan D., Sever M.S.* Cardiac and intestinal amyloidosis in a renal transplant recipient with Familial Mediterranian fever. J. Nephrol. 2001; 14 (2): 125-127.