Department of Pathology of the István Hospital *(Director: J. Vikol)*, 3rd Department of Medicine *(Director: Prof. P. Gömöri)* and Section of Pathology of the 3rd Department of Surgery of the Medical University *(Director: Prof. P. Rubányi)*, Budapest

THROMBOTIC THROMBOCYTOPENIC PURPURA (MOSCHOWITZ' SYNDROME)*

B. Radnai, L. Takács-Nagy, I. Szigeti, and *P. Endes*

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In 1925 *Moschowitz* [13] reported a case of acute febrile pleiochromic anaemia in which extensive hyaline thrombosis of the arterioles and capillaries occurred. *Moschowitz* considered the condition to be an up to then unknown haematologic disease. *Baehr, Klemperer* and *Schifrin* pointed out that thrombocytopenic purpura was also a characteristic symptom of the disease [3]. The term thrombitic thrombocytopenic purpura was suggested by *Singer* and al. [19]. To date, 36 cases have been published under various names. Mostly young women are affected by the disease which is frequently preceded by a catarrh of the upper respiratory tract. At the onset, weakness, fever and pains in the joints appear, to be followed later by splenomegaly, haemolytic anaemia with jaundice, thrombocytopenia, leucocytosis, than focal symptoms in the heart, kidneys, and mainly in the nervous system. The disease cannot be influenced and ends fatally in 2 to 8 weeks. As for the anatomic changes, the disease is marked by thrombosis in the arterioles and capillaries of all organs. The thrombi have been regarded ever since the first publications as consisting of platelets. In Hungary, no such case has been reported up to the present.

Report of Cases

Case 1. A woman aged 28 was admitted to an obstetrical department for abnormal menstrual bleedings on November 29, 1949. The bleeding could not be controlled by curettage. Histologic examination of the curetted material did not reveal pregnancy, nor was any abnormality of the uterus found. After curettage headache on the right side occurred on the fourth, paresis of the facial nerve and of the left arm on the fifth day. At the same time the patient complained of cribbling sensations in her entire left side, and she ran a temperature. A tentative diagnosis of septicaemia was made and the patient referred to a medical department for examination. There she remained for some hours only. Her temperature was 38° C, the blood pressure 140/80 mm Hg, she had nausea, vomited, and complained of blurred vision. In the nervous system no paresis or pathologic reflexes were found. The knee jerk was slightly increased and the pupils reacted somewhat weakly to light. Because of the persisting bleeding from the uterus and the increasing anaemia, the patient was forwarded to the department of gynaecology of the hospital for suspicion of a septic abortion. This was on the 9th day of the

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disease. Then she ran a temperatures of 37° to 39°, she had intensive headaches and, later disturbed sensorium. Apart from the bleeding, no abnormality was found in the genital organs. The blood counts revealed 1 600 000 erythrocytes, 4200 white cells, out of which 45 per cent were lymphocytes, 34 per cent polymorphonuclears, 15 per cent stabs, 5 per cent monocytes, and 1 per cent eosinophils. She was given a transfusion of group 0 blood, penicillin, and cardiac drugs. Subsequently she became unconscious, developed heart failure and died on the 13th day of the disease. The tentative diagnosis was septicaemia (?), haemorrhagic endometritis, and acute heart failure.

At *autopsy*, anaemia was found with numerous petechiae in the myocardium, the subendocardial tissue, the submucosa of the stomach and the bowels. The spleen weighed 200 g, it was bluish red, soft, non-pulpous, with well visible follicles on the cut surface. In the other organs no change could be seen with the naked eye. The endometrium was slightly haemorrhagic. The parametrium was intact on both sides. The brain exhibited anaemia and oedema. Two thirds of the femur contained a red bone marrow.

Histology unexpectedly revealed thrombi in nearly all the small vessels of practically every organ, especially the myocardium, adrenal cortex, medulla oblongata, and kidneys. In the myocardium, not infrequently 8 to 10 small thrombi were present per visual field (Fig. 1). Strikingly, none of the thrombi had given rise to complete obstruction of the vessel. Between the thrombus and the wall there always remained a thin space, in which intact corpuscular elements were present. The structures of the thrombi varied. In the majority, signs of organisation occurred, the homogeneous substance containing fibroblasts and, on the surface opposite the lumen, endothelial cells (Fig. 2). Here and there thrombi consisting of loose filamentous fibrin and platelet-like granules were found without the signs of organisation (Fig. 3). The calibre of the thrombosized vessels corresponded mostly to precapillary arterioles. The vessel wall, however, was of a different structure, there being no, or at most a very thin layer of smooth muscle. Where a thrombus adhered to the vessel wall the latter became homogeneous, nearly confluent with the thrombus. Around the thrombosized vessels some haemorrhages occurred. Finally, extensive thrombosis was present in the zona glomerulosa of the adrenal cortex (Fig. 4).

These phenomena suggested that thrombosis affected vessels which had previously undergone a morbid change. No hyalinosis or other pathologic alteration was found in the wall of vessels unobturated by a thrombus. Attention should be called to the fact that vascular changes were found only in the parenchyma of the organs, whereas their capsule and environment were unaffected. Nevertheless, the parenchyma suffered but slight lesions, probably due to the fact that the obturation was incomplete.

Similar, but less severe alterations than those of the myocardium and the adrenal glands could be observed in the kidneys in which the afferent arterioles were partly filled with recent or organized thrombi. Several thrombosized vessels were seen in the medulla oblongata, especially in the nucleus olivaris, whereas in other parts of the brain (parietal cortex, hypothalamus), further in the liver, spleen, and the anterior pituitary, no thrombi were found. The bone marrow contained many megakaryocytes which were believed to be a sign of increased thrombocyte destruction and subsequent regeneration.

Case 2. A 33 years old woman was admitted to the 3rd Dept. of Medicine of Budapest Medical University, on May 21, 1952. Prior to this, the patient had been treated in the Dept. of Surgery for a fracture of the right tibia. The fracture had healed without complications but then the patient developed fever and anaemia, wherefore she was transferred to the Medical Department. It was revealed in the history that for several months she had felt weak and tired, and unwell when walking or working. Her temperature had not been taken before the accident but during her stay at the Dept. of Surgery she had temperatures up to 38,5° C. At present she ran similar temperatures. The blood pressure was 110/80 mm Hg, the urine was normal. Blood counts revealed 1 900 000 erythrocytes, 39 per cent haemoglobin, 8400 white cells, 6000 platelets. The differential count showed some immature forms and a few normoblasts. The reticulocyte count was 4,2 per 100 cells, the sedimentation rate 120 mm per hour, the bleeding tome 28 min. 30 secs ; coagulation time 7 min. 50 secs ; retraction of the platelets did not take place even after 24 hours. The sternal bone marrow was rich in cells, with increased erythropoiesis and myelopoiesis, a considerable shift to the left, and toxic granulation in the myeloid elements. Many megakaryocytes and marked inhibition of the maturation process were observed. There was a considerable numerical increase in lymphoid and plasmacellular reticulum cells. The liver reached two fingerbreadths below the costal arch. The spleen was just palpable, its upper pole was, in the mid-axillary line, in the 8th intercostal space. On admission the patient was jaundiced. During her stay a gradual deterioration of the general condition ensued, and then suddenly a disturbed state with psychic and motor restlessness occurred. She had choreiform and athetotic motions. The lower extremities displayed signs of a pyramidal lesion which subsequently ceased, only to reappear again. Later, haemorrhages appeared on the skin and the mucous membranes.

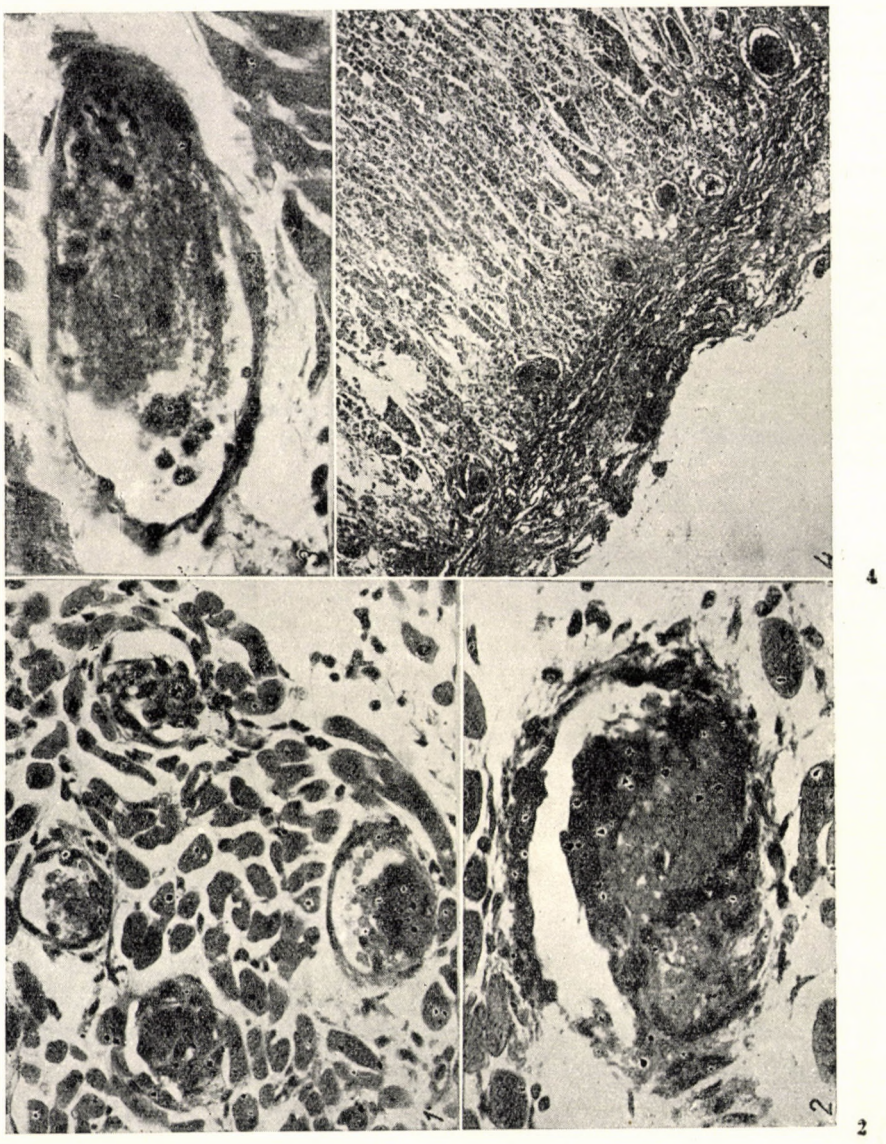

Fig. 1. Tiny parietal thrombi in most of the precapillary arterioles of the myocardium. Partial obstruction of the lumina. Case 1. Haem.-Eos. stain. ×90

Fig. 2. Thrombosized arteriole in the myocardium. At its attachment the structure of the vessel wall has disappeared and fused with the thrombus. There are fibroblasts in the thrombus and endothelial cells on its surface. Case 1. Haem.-Eos. ×360

Fig. 3. Early, loosely woven granular thrombus in myocardial arterioles. It adheres to a thicker part of the vessel wall. No endothelial covering. Case 1. Haem.-Eos. ×360

Fig. 4. Numerous thrombosized arterioles in the zona glomerulosa of the adrenal cortex. Case 1. Azan. ×72

Haemorrhagic stripes were seen on the eye fundi, especially around the papillae. Menstruation was unusually copious. With time the jaundice became more intensive. Serum bilirubin was 8,9 mg per 100 ml, giving an indirect reaction. Prior to death, RBC was 1 400 000, with 30 per cent haemoglobin, 12 600 WBC, 5000 platelets. In the last days apathia, stupor, and a negativistic psychic state developed, alternating with deep loss of consciousness, motor restlessness, and hyperkinesis. The patient died on May 31, 1952.

At *necropsy*, marked jaundice was present and extensive haemorrhages were found over the whole body, on the mucosa of the trachea, stomach, bowels, below the epi- and endocardium. There was fatty degeneration in the myocardium. The spleen was enlarged, soft, pulpous : the liver enlarged, fatty, saffron coloured, icteric. The kidneys were yellowish brown, soft. There was a small apple-sized haematoma in Douglas' cavity and some blood in the right Fallopian tube. The meninges were hyperaemic, their interspace contained blood on the convexity. The brain was also hyperaemic but no change was seen in its substance. In the lower third of the right tibia a healed transverse fracture was found. Red bone marrow was present in the shaft bones.

Histology. In the stem ganglia some capillaries were obturated by homogeneous thrombi staining red with eosin. The endothelium was swollen, proliferating, invading in some places the thrombi (Fig. 5). The structure of the spleen was indistinct, the pulp full of erythrocytes. The liver showed centrilobular fatty degeneration, accumulation of bile pigment, and early necrosis of the liver cells. In many places the small branches of the hepatic artery and the capillaries displayed aneurysmlike dilatations filled with thrombi (Fig. 6). In the vascular walls deposition of a hyaline mass was seen. This deposition had apparently given rise to dehiscences through which the hyaline substance had entered into the perivascular connective tissue. In some areas the hyaline substance was uncovered by endothelium and lay free within the lumen and became covered by a thrombus. In the kidneys the epithelium of the proximal convoluted tubules showed severe degeneration turning into necrosis. In the lumina of the tubules, bile pigment and erythrocyte casts were present. Most arterioles and capillaries contained thrombi. At many sites proliferation of the endothelium had started without thrombosis and led to the obstruction of the lumen. Around the vessels fibroblasts, and in some areas granuloma formation were seen. In part of the arterioles no thrombi were present. Their wall was, however, thickened by hyaline (Fig. 7, 8). Some vessels underwent complete destruction whereby the hyaline mass partly forming the wall became released into the surrounding tissues. In some glomeruli thrombi were present, while in others the basal membrane was thickened, or proliferation of the endothelium and of the epithelium in Bowman's capsule was observed. Some glomeruli have been replaced by granuloma. The glomerular changes were not diffuse and the iuxtamedullary glomeruli were mainly involved. The bone marrow exhibited myeloid metaplasia, hyperaemia, and haemorrhages.

Discussion

It is clear from the above case reports that their morphology corresponded to the syndrome described by *Moschowitz* and others. The same was shown by the clinical course. Final evidence has, however, been gained only from histology. Hyalinosis of the small vessels in various organs, the consequential early and organized thrombi, the haemorrhages and the few small aneurysms, were common features in earlier cases. The morphologic signs described allow some conclusions as to the pathogenesis and the pathomechanism of the syndrome. The value of the observations is chiefly due to the fact that we had the opportunity to examine, and compare, the acute form of the disease resulting in death within two weeks with a chronic case lasting for about two months. In this way the morphologic changes could be traced from the onset to their final development.

The primary histologic change consists, in our opinion, in a deposition of a hyaline substance in the intima of the arterioles, on which the subendothelial argyrophilic membrane remains initially preserved. It follows that the change observed is a primary lesion of the vessel and not a herniated thrombus. Sub-

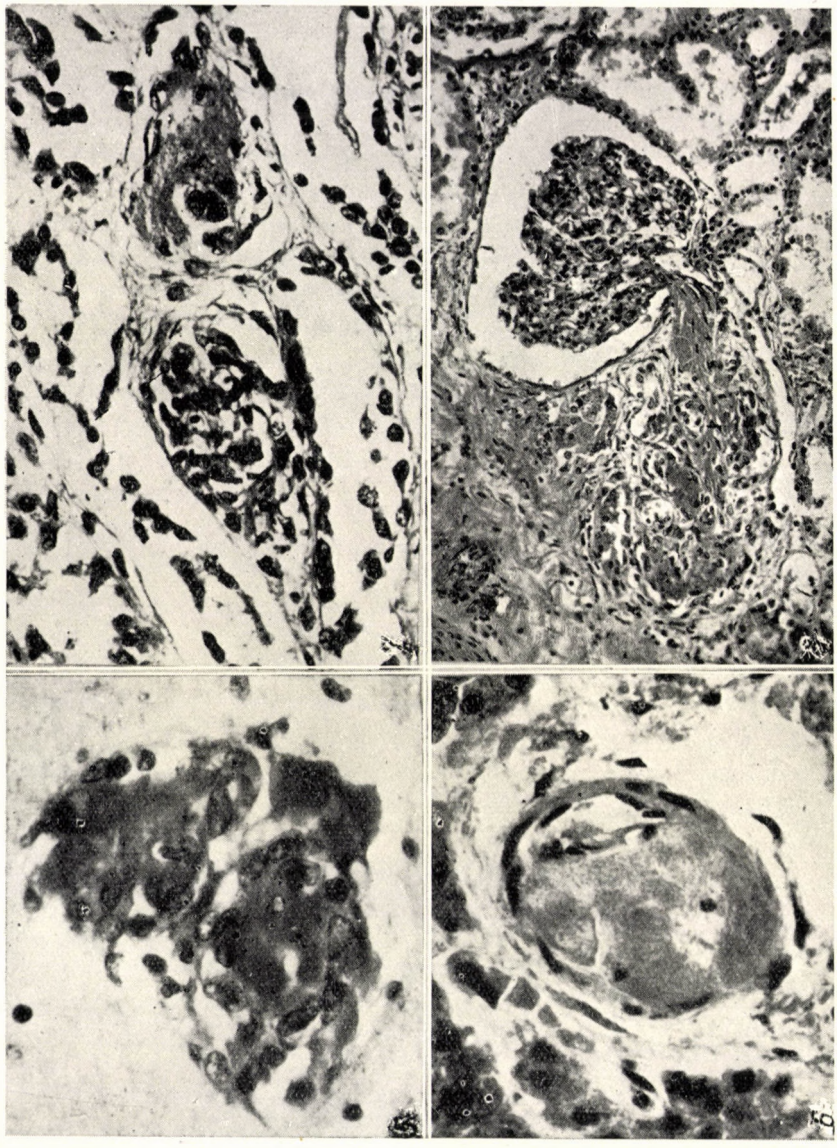

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Fig. 5. Two adjacent capillaries in the brain. Obstruction of the lumina by homogeneous thrombi. Swollen, proliferating endothelium. The homogeneous substance is present also outside the vessel. Case 2. Haem.-Eos. ×400

Fig. 6. Aneurysm-like dilatation of a hepatic arteriole. Loosely woven thrombus with two leucocytes in the lumen. The latter is a narrow gap. Haem.-Eos. ×400

Fig. 7. Two renal arterioles. No thrombi. The lumen of one of them is completely obstructed by proliferating endothelium. In the other necrosis of the wall. Haem.-Eos. ×400

Fig. 8. The wall of the afferent arteriole next to the glomerulus is homogeneously thickened. Around the vessel a granuloma consisting of proliferating endothelial cells and fibroblasts. Haem.-Eos. ×100

sequently, the process extends towards the lumen, the endothelium undergoes destruction and a thrombus is formed. According to the findings in Case 1, the early thrombus is made up of a granular substance, probably platelets adhering to each other, as it has been stated by some authors [4, 6, 8, 10] on the basis of the structure, the histochemical and staining reactions. The granular structure soon disappears and the thrombus becomes homogeneous. This is why the latter form is the one far more frequently observed and why the original structure of the thrombus is still being debated. *Allen* [1] believes that the thrombi consist of clotted plasma. On the basis of our observations the original opinion, according to which the thrombi are made up of platelets, should be adopted. With time the homogeneous thrombus undergoes organisation, its surface becomes covered with an endothelial layer. Following destruction of the internal elastic membrane the hyaline mass may invade the outer layers of the vessel, the vessel wall bursts and haemorrhage ensues. The diseased section of the vessel wall becomes frequently dilated like an aneurysm. In our second patient the aneurysms occurred at the arterio-capillary junction, as it has been demonstrated by *Orbison* [15] by means of plastic reconstruction of the vessel. The necrosis of the vessel wall is accompanied by proliferation of the surrounding fibroblasts and thus a perivascular granuloma containing no inflammatory elements is formed. As a rule, the obstruction of the arterioles is, like in our cases, incomplete : necrosis of the parenchyma is, therefore, a rare incidence.

As mentioned above, the morphology of our cases supports the view that the vascular changes are the primary ones. This view is supported by the fact that, in our Case 2, vessel wall destruction occurred at several places in the kidneys without thrombosis, and further that the swelling and proliferation of the endothelium gave rise to formation of a granuloma-like structure. There is a certain similarity between these vessel changes and the lesions of the glomeruli in acute focal nephritis. The minute thrombus in both diseases formed at the site of an endothelial lesion, in a dilated capillary. The process is then followed by pericapillary haemorrhages, respectively haematuria.

In a contrast with our view regarding the vessel lesions as primary changes, many authors contend that pathological clotting is the essential factor of the disease [7]. According to this, increased agglutination of the platelets would be the primary phenomenon, followed by secondary changes of the vessel wall in the vicinity of the thrombus. None of our observations gives any support to this presumption. The severe anaemia of the patients, their mild jaundice, and the hyperplastic bone marrow, have been referred to as arguments by several authors. In our opinion, these phenomena are of toxic origin, probably due to the same agent as the changes of the vessel wall. There is little evidence that the numerical decrease of the platelets is due to multiple thrombus formation. On the other hand, the lack of antithrombin activity associated with normal thrombin activity may also result in thrombosis. In our cases, and also in those

reported in the literature, the bleeding time and the time of clot retraction were considerably, the clotting time slightly, prolonged.

Gitlow and *Goldmark* [9] pointed out as early as in 1933 that the syndrome under discussion should be listed with disseminated lupus erythematodes, Libman—Sacks' syndrome, and periarteriitis nodosa. Presently, it is grouped with the so-called collagen diseases [20, 21]. In differential diagnosis, first of all lupus erythematodes and Libman—Sacks' syndrome should be distinguished from Moschowitz' syndrome, anaemia, thrombocytopenia, purpura, and renal changes being common features in all of the three conditions. In lupus erythematodes there is, however, leucopenia, the glomeruli exhibit the characteristic wire-loop symptom, and, beside the arterioles, the small arteries are also involved. Similar arterio-capillary thromboses occur in rickettsial diseases, especially in epidemic typhus [23,] but these may be recognized on the basis of the perivascular inflammatory infiltration and the serologic tests. Some resemblance may be found with periarteriitis nodosa, especially with regard to the clinical course, the morphological pattern and a few features of the pathogenesis. Still, the fact that the hyalinosis and necrosis of the arterioles, observed by us in collagen disease and rheumatoid arthritis [17], do not result in thrombosis, suggests that in the pathomechanism of the vessel changes occurring in Moschowitz' syndrome factors also other than those hitherto recognized might play a role. Again the result of *Orbison* [16] should be quoted, who induced in dogs diffuse arteriolar necrosis attended by symptoms of malignant hypertension and observed the formation of parietal thrombi at the places of necrosis, like in Moschowitz' syndrome.

The clinical symptoms of the syndrome depend on the localization of the vessel changes. This is again a common feature of Moschowitz' syndrome and periarteriitis nodosa. In the opinion of many authors, changes in the myocardium and in the central nervous system play a decisive part. In our Case 1 the severe thrombosis of the arterioles of the adrenal cortex deserves all the more attention, since this localization has not been mentioned by other authors. We believe that this change has played a prominent role in the development of the clinical picture and the fatal outcome. In our Case 2 the most severe changes occurred in the kidneys, like in other generalized diseases of blood vessels. It was striking that the juxtemedullary glomeruli were mainly affected. With regard to the granulomas around the afferent arterioles and the glomerulitis observed at the corticomedullary border, the role of allergic factors was also taken into consideration.

As to the aetiology of the syndrome, almost nothing has been learned. It has been assumed that, like in collagen diseases, the changes are due to an unknown exogenous or endogenous toxic agent or that they are produced by an allergic mechanism. In the history of the published cases hypersensitivity reactions, drug allergy, or subacute glomerulonephritis had frequently occurred [10, 14]. Similar vessel changes associated with thrombocytopenia and agglutina-

tion of the platelets occur in pepton schock and anaphylaxis and with Schwartzman's phenomenon. This would speak for an allergic-hyperergic origin. In our cases, however, not one single fact was found to clarify the aetiology of Moschowitz' syndrome, by some allergic mechanism or by any other approach.

Summary

Two cases are reported in which generalized arteriolo-capillary thrombosis associated with fever, haemolytic anaemia, thrombopenic purpura, and nervous symptoms occurred. One of them took an acute, the other a chronic course. The morphology of the syndrome is discussed in detail. The degenerative necrotizing changes of the small arteries are held to be primary, the thrombosis is considered secondary. The syndrome is listed with the generalized necrotizing diseases of blood vessels and its relations to collagen diseases is pointed out. The most striking changes occurred in the heart and the adrenal glands of Patient 1, and in the kidneys of Patient 2. These changes might have played a role in the development of the clinical symptoms. As to the aetiology, nothing could be learned in either of the cases. Unknown toxic agents and the changed reactivity of the organism may have taken part in the development of the symptoms.

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ТРОМБОТИЗИРУЮЩАЯ ТРОМБОПЕНИЧЕСКАЯ ПУРПУРА (СИНДРОМ МОШОВИЦА)

Б. Раднаи, Л. Такач-Надь, И. Сигети и П. Эндеш

Резюме

Авторы описывают острый, или же затянувшийся случай двух генерализированных артериолокапиллярных тромбозов, сопровожденных лихорадкой, гемолотической анемией, тромбопенической пурпурой и симптомами в нервной системе. Подробно описываются морфологические особенности, среди которых авторы считают первичным дегенеративно-некротизирующее изменение мелких кровеносных сосудов, в то время как тромбозы рассматриваются вторичным заболеванием. Авторы относят вышеприведенные процессы к генерализированным некротизирующим болезням кровеносных сосудов и указывают на родственные черты с т. н. коллагенным заболеваниям. В первом случае изменения показались выраженнее всего в надпочечниках и в сердце, а во втором случае в почках. Этим изменениям следует придавать большое значение и при оформлении картины болезни. Этиологию не удалось ни в одном случае выяснить. По всей вероятности при возникновении изменений играют роль неизвестное токсическое повреждение и измененная реактивная способность организма.