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Moschcowitz Syndrome with Involvement of the Central Nervous System

Light Optical Studies on the Genesis of Hemolytic Anemia and Vascular Changes

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Summary. The origin of hemolytic anemia, the histogenesis of vascular changes and the origin of prethrombotic lesion are dicussed in a typical case of thrombotic thrombocytopenic purpura (TTP) with early neurological symptoms. The disease arose after exposure to a chloronaphtalene containing substance. In addition to the typical vascular changes of different age, early non-endothelialised and non obstructing aggregates of fibrin and thrombocytes are observed. Clusters of drop-like deformed erythrocytes and elongated leucocytes are attached to their surface. These changes do not appear to have been reported previously in TTP. The fresh thrombi are regarded as being hematologically active. Support for their supposed causal relationship to hemolytic anemia is given by experimental data by Brain and Bull.

Key words: Thrombotic-Thrombocytopenic Purpura — Moschcowitz Syndrome — Hemolytic Anemia — Prethrombotic Lesion.

Thrombotic-thrombocytopenic purpura (TTP), first described by Moschcowitz (1925) is characterised throughout the body by hyaline thrombi in the arterioles and capillaries without any inflammatory lesions of the vessel (Adam *et al.*, 1948). The disease may occur at any age (Monnens and Retera, 1967). The etiology and many pathogenetic problems are obscure. Some otherwise typical cases have been demonstrated to be Lupus erythematodes by positive LE-tests (Levine and Shearn, 1964; Lusher *et al.*, 1968). However, other immunological findings have not been observed so 1ar. Coomb's tests for erythrocytes and thrombocytes are usually negative (Amorosi and Ultman, 1966). The nature of the thrombi is questionable: Moschcowitz (1925) regarded them as agglutinated erythrocytes while Gore (1950) and others believed them to be thrombocytes. Later, while no thrombocytes could be identified (Feldmann *et al.*, 1966), both fibrin and IGG were detected by immune histochemical methods (Craig and Gitlin, 1957; Feldmann *et al.*, 1966). Limited electron microscopical examination showed subendothelial and intramural, fibrin-like (Feldmann *et al.*, 1966) or amorphous material (Dunea *et al.*, 1966). The first apparent change ist the so-called prethrombotic lesion (Gore, 1950), a homogenous, acidophil, PAS positive, subendothelial deposit, extending into lumen in some places and providing the prerequisites for secondary clotting. The prethrombotic lesion usually occurs at the arteriolo-capillary level, but the type of vessel affected can be identified only in serial sections, because aneurysms may occur in them (Orbison, 1952). The clots are usually covered by endothelium and endothelial cell proliferations with

mitoses (Adam *et al.*, 1948). The hemolytic anemia commonly associated with TTP has been interpreted as being of microangiopathic origin (Brain *et al.*, 1967a, b, 1968). It has been argued that erythrocytes are injured either mechanically or chemically at sites of damage to the vessels and hemolysis ensues. This suggestion is supported by the typical blood-smears (Brain *et al.*, 1967; Levine, 1970), and a greatly reduced survival period of erythrocytes (Amorosi and Ultmann, 1966). On the other hand the presence of Heinz-bodies (Diewitz *et al.*, 1966) and the reduced survival period of TTP erythrocytes in other patients are in favour of a corpuscular genesis of the hemolytic anemia. The thrombopenia, characteristic of TTP, is believed to be due to increased consumption of thrombocytes (Amorosi and Ultmann, 1966). As a lack of platelet shedding in megakaryocytes, normal or increased in number is frequently observed, a disorder in thrombocyte formation also seems possible (Barnhard *et al.*, 1964). The problem of consumption coagulopathy (Castleman, 1968) and its relation to a generalised Schwartzman phenomenon have not been elucidated (Pappas *et al.*, 1958). Increased (Barnhard *et al.*, 1964), normal or reduced (Amorosi et Ultmann, 1966) fibrin levels and turnover as well as abnormal fibrin (Rivero and Ritz, 1968) have been reported.

Case Report

H. L. a woman of 56, had meningitis at 17. Aged 45 she had a hyterectomy for preinvasive carcinoma. Five days before the present admission to hospital she had painted a bench with varnish containing chloro-naphthalene (Xylamon Lasur). Some hours later ecchymoses appeared on the uncovered parts of her skin. Two days later she developed nausea, jaundice and transitory paresis of her left arm. Examination: she had hemolytic anemia—red cell count 2300000, hemoglobin 7.7 mg-%, MCHC 33.4%, reticulocytes 12%, platelets 60000, indirect serumbilirubin 3.0 mg-%, LDH 519 mU, serum iron 170%, free hemoglobin 31 mg-%, ahaptoglobinemia and normal mechanical resistance of red blood cells. The Steffen Test revealed no antibodies to platelets or to thymus. Urine analysis: Uroporphyrin positive, coproporphyrin and porphobilinogen normal, no bilirubun. Bone marrow smear: Erythropoiesis increased-macronormoblastic, granulopoiesis decreased; Megakaryocytes showed the normal stage of maturation but no shedding of platelets. LE cell preparation negative. Neurological examination: signs of a midbrain lesion caused probably by tentorial herniation. Fundi: hemorrhages at the periphery, no papilledema. For two days the patient received prednisolone 40 mg/day, after that 120 mg/day. On the 9th day she developed grand mal seizures and finally died in coma, 21 days after the first clinical symptoms.

Clinical diagnosis: "neuro-hemolytic syndrome".

Post Mortem Examination

There was generalised jaundice, ecchymoses were present on both arms. The internal organs were normal. An old temporobasal infarction was present on the left side of the brain. The myocardium, liver, spleen, kidney, bone marrow, brain and spinal cord were examined histologically. Parts of the formalin-fixed brain were postfixed in glutaraldehyde and then in osmium tetroxide and embedded in epon: Semi-thin sections were stained with toluidine blue. The vessels (Arterioles and capillaries) of all the tissues examined showed proliferation of the endothelial cells and cóntained eosinophil masses (Fig. 1 B–D). These eosinophil deposits were both subendothelial (1) and intraluminal (2) and are described separately.

1. Eosinophil masses which prodruded into lumen and were covered and surrounded by endothelial cells some of which were in mitosis. The masses were often

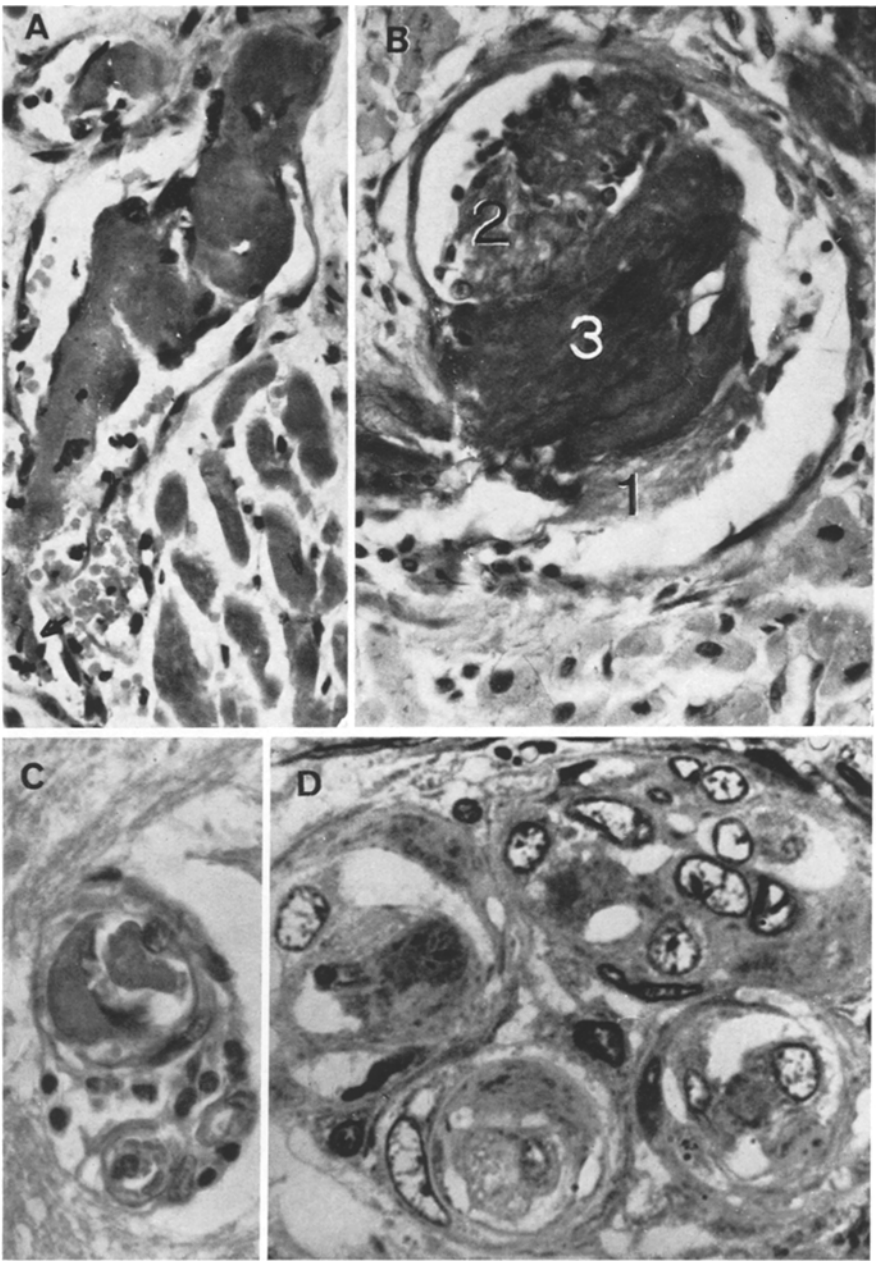

Fig. 1. (A) Myocardium, longitudinal section through an aneurysm of a blood vessel with a free floating thrombus partly covered by endothelium. In the left lower corner, the youngest part of the thrombus presents elongated leucocytes (arrow). H.E. ×340. (B) Myocardium, an almost occlusive thrombus shows three parts: more recent deposits (*1, 2*) on either side of the central older fibrin thrombus (*3*). PAS × 375. (C) Typical vascular changes with hyaline clots in the pons. PAS × 630. (D) Partly obstructed vessels with endothelial proliferation in the pons, Semi-thin section. Tol. blue × 1800

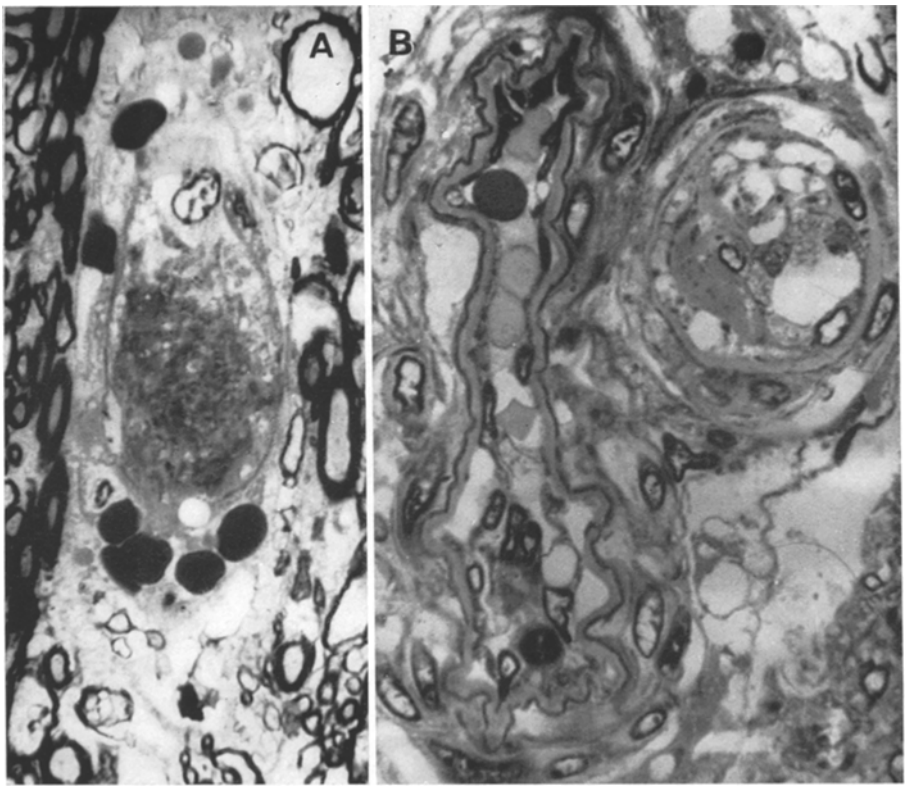

Fig. 2. (A) A fresh obstructive thrombus surrounded by extruded erythrocytes; disintegration of myelin occurs in perivascular edema. Semi thin section from the pons, Tol. blue × 1260. (B) A small artery on the left with multiple plasmorrhagias into the vessel vall and activation of endothelial and adventitial cells. Recanalises artery on the right. Semi thin section from the pins, Tol. blue × 1250

large so that the vessel presented a slitlike lumen (Fig. 1A, 1B, 1D). Sometimes the masses extended into the periadventitial tissue, destroying the vessel wall, or they might extend only, beyond the internal elastic lamina. Some masses were separated into two or three parts between which were occasional endothelial cells (Fig. 1B). The masses had a fibrillar or a granular structure especially when stained with PAS. Older deposits were denser and stained more intensively with eosin than more recent ones. In some places homogenous subendothelial deposits occured and represented the so called prethrombotic lesion (Gore, 1950). In our case this lesion could be identified only by its homogenous structure and not by any staining characteristic.

2. Eosinophil aggregates consisting probably of fibrin and platelets were not covered by endothelium and did not block the lumen completely. On their surface were clusters of drop like deformed red blood cells and elongated white blood cells with thread-like nuclei which were Feulgen positive (Fig. 1A). These aggregates obviously seemed to be fresh thrombi. Their development and the cause of

their subendothelial or intraluminal occurence can be observed in longitudinal section (Fig. 1A): the oldest part is attached to the vessel wall and covered by endothelium without any obvious connection to a prethrombotic lesion. Along the direction of the blood flow, which can be concluded from the arrangement of trapped blood cells, the thrombus becomes less compact and an endothelial covering is no longer found. Free floating aggregates of fibrin and platelets represent the most recent part, the tip of the thrombus. On its surface clusters of elongated leucocytes and red blood cells are trapped. The affected blood vessel is widened with rarefaction of its wall. Numerous red blood cells throughout the vessels are deformed and fragmentated (burr cells, schistocytes) (Levine, 1970). Many erythroblasts are found in the vessels indicating increased erythropoiesis.

The organs presented the following peculiarities: the myocardium showed the most marked, typical vascular changes, many of the vessels being occluded by thrombi and some were recanalised. Infarctions of various ages were present throughout the myocardium. The liver showed lymphocytic infiltration of the periportal spaces. The Kupffer cells were swollen and showed phagocytosis of erythrocytes and of nuclear fragments. The spleen which was congested showed severe involvement of the vessels including the capillaries of the pulp. Some megakaryocytes were present in the spleen. The afferent vessels of the kidney were intensively affected and some glomerular capillaries presented fibrin thrombi. In the tubules there occurred protein and casts of red blood cells. Many schistocytes occurred in the small veins. The bone-marrow showed active erythropoiesies. Many megakaryocytes present had smooth surfaces. Some erythrophages occurred. The leptomeninges showed very few typical vascular changes. Disseminated hemorrhages of different age occurred throughout the brain. The cerebral cortex was severely affected by typical vascular changes, consisting of subendothelial deposits protruding into the lumen and proliferation of endothelial cells. Only one small recent infarction occurred. The vessels in the white matter of the cerebrum are little affected but the cerebellar cortex and dentate nucleus more so. The brain stem was most intensly affected by typical vascular changes (Figs. 1A, 1C, 2D, 2A, 1B) with many foci of necroses, perifocal edema and axon swelling. The spinal cord showed severe affections of the gray matter by typical vascular changes, but did not present infarctions or hemorrhages.

Discussion

Having observed impressive clusters of elongated leucocytes we then found fresh thrombi, which were not endothelialised, but floated freely in the vessel lumen and did not obstruct it completely. They were formed of loose aggregates of fibrin and platelets. On closer inspection of these deposits, clusters of deformed erythrocytes were seen attached to their surface (Fig. 1A). This observation is in accord with the experimental findings of Brain *et al.* (1967, 1968) and Bull and Kuhn (1970) on microangiopathic hemolytic anemia and leads us to believe that hemolytic anemia in Moschcowitz-Syndrome is caused by damage of the red blood cells by fresh thrombi. We therefore called these thrombi "hematologically active". To our knowledge elongated leucocytes with thread-like deformed nuclei have not yet been reported in this context. Most of the subendothelial deposits in

our opinion represent intraluminar thrombi freshly covered by endothelium. The origin of those deposits from platelets was postulated on morphological grounds by former investigators (Gore, 1950) but this hypothesis was then abandoned because of negative histochemical and immune-histochemical findings (Craig and Gittlin, 1957). Feldmann *et al.* (1966) mentioned that platelets could be observed ultramicroscopically but could not be identified by immune-histochemical methods. Lapp (1971) studying endotoxin shock demonstrated viscous transformation and rapid disintegration of platelets within less than one hour. In our opinion platelets do take part in the formation of thrombi, but because they disintegrate rapidly and are masked in the surrounding fibrin they cannot be identified in the thrombi. Therefore, thrombopenia in TTP is probably caused by the consumption of platelets in numerous thrombi. An additional alteration mechanism of the platelets similar to that of erythrocytes has to be considered. Thus megakariocytes with smooth surfaces may not represent an inactive state. Injury to the vessel wall has been dicussed repeatedly as cause of thrombogenesis (Lechler *et al.*, 1969) and Orbison (1952) claimed that it was the cause of aneurysmal expansion. Gore (1950) believes that the prethrombotic lesion initiates thrombosis. In our case the prethrombotic lesion was particularly impressive within the myocardium. Surrounding the lesion there were small subendothelial hemorrhages mimicing the prethrombotic lesion in shape, position and extension. This leads us to the opinion that the prethrombotic lesion could arise from these hemorrhages, which the coagulate to form the homogenous deposits. This indicates that the endothelial lining must have been damaged either by alternation of the cells themselves or of their intercellular junctions. These cement lines (maculae occludetes) are dependent on the quantity and functional state of the platelets (Gore *et al.*, 1970). Therefore the prethrombotic lesion might be a symptom of thrombocytopenia; we could not confirm the findings of Gore (1950) showing a connection between the prothrombotic lesion and intravascular clotting. Ultrastructural findings may indicate endothelial cell damage (Feldmann *et al.*, 1966). However the enormous proliferative potency of the endothelial cells makes primary endothelial damage unlikely. The Moschcowitz syndrome seems to result from a variety of etiological processes. Spontaneous intravascular clotting, primary endothelial alteration and microembolisation by amnion fluid or tumor cells lead to a similar appearence and result in a identical pathogenetic process of intravascular clotting with consumption of fibrin and platelets and damage to erythrocytes on the surface of non-obstructive thrombi. The result are thrombocytopenia, hemorrhagic diathesis and hemolytic anemia. Deposition of thrombi progresses slowly and stepwise; re-endothelisation lags behind the formation of new clots. Therefore consumption of fibrinogen is detected in most cases from increased fibrinogen exchange only (Brain *et al.*, 1967, 1968). In very slowly progressing cases the fibrinogen level is increased as a compensation (Barnhard *et al.*, 1964). The results of vascular obstruction depend upon the degree to wich different organs are affected. Massive involvement of the kidney leads to the hemolytic uremic syndrom, (Dunea *et al.*, 1966, and Hinton, 1968) and affection of the lung to cor pulmonale acutum. Torpid ulcers are the result of cutaneous affection. The small amount of blood passing through the skin may explain the absence of anemia, in some cases (Krey and Ley, 1967). If thrombi are equally

disseminated in all organs, damage to the brain causes the leading clinical symptoms. Besides the previously mentioned etiological factors, toxic and therapeutic influences are often discussed (Paz *et al.*, 1969). In our case the appearance of the first clinical symptomes two hours after using a chloronaphtalene containing varnish is very impressive.

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