PROLIFERATIVE INTIMITIS OF SMALL ARTERIES AND VEINS ASSOCIATED WITH PERIPHERAL NEURITIS LIVEDO RETICULARIS AND RECURRING NECROTIC ULCERS OF THE SKIN

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The various types of occlusive vascular disease produce clinical pictures which may vary greatly with the extent and location of the lesions and the rapidity with which they develop. However, certain clinical and pathological entities have been established and although their exact etiology still remains obscure, the diagnosis usually is not difficult. This case is presented because of its unusual clinical and pathologic features which do not conform to any of the more common syndromes. One of the outstanding features of the case was the marked degree of livedo reticularis; this is a descriptive term which has been given to a permanent bluish-red, retiform mottling of the skin of the extremities and frequently the trunk also.

According to Williams and Goodman, the basis for livedo reticularis, also called livedo reacemos and generalized telangiectasis, is a capillary dilation or atony which may be primarily functional or may be associated with congenital vascular anomalies or organic disease of small arteries and veins. In 1893, Unna reported a case with mutliple ulcers and "chronic phlebitis." Endarteritis and endophlebitis of small arteries and veins have been found in skin biopsies from cases of livedo reticularis by Stokes, Urbach, Becker and Ebert. Periarteritis and periphlebitis have also been noticed occasionally. No extensive pathologic studies of larger vessels and nerves have been described.

Theetiology of the vascular lesion in various case reports ascribed to syphilis (Ehrman) arteriosclerosis (Gross and Kerl) tuberculosis of the erythrma induratum type (Williams and Goodman.) Stokes, Becker and Ebert have reported cases in which no etiologic factory was apparent. Associated ulceration of the skin

was noted also in Ebert's case. The combination of livedo reticularis, recurrent indolent ulcers, severe intractable pain, and acute arterial occlusion of the toes has not been ascribed.

CASE REPORT

History:

[redacted], age 34 years, formerly a machinist, first came under the observation of the Mayo Clinic in October, 1932. Eight years prior to his visit, a diffuse reticulated purplish mottling had gradually developed over all the extremities and to a lesser degree over the trunk. This condition was more noticeable over the lower extremities and was markedly aggravated by cold. A short time after the onset, a series of painful sloughing ulcers developed on both legs, the usual site being the lateral aspect of the ankles. The patient said that these ulcers developed without preceding nodules but always in one of the blue patches. New ulcers never appeared simultaneously on both legs. Healing usually occurred within fourteen to sixty days, regardless of the therapy employed, leaving an atrophic pigmented scar. The Wasserman reactions of the blood and spinal fluid elsewhere had been negative. In 1928, four years after the onset, while working with white lead as a lubricant, he had developed a left peroneal palsy, at which time lead had been found in the stools and urine, and basophilic stippling in the erythrocytes. The foot drop disappeared spontaneously when contact with lead was ended, and there had been no recurrence nor did this episode seem to influence the mottling of the skin or development of ulcers of the leg.

The patient had also been the victim of two severe attacks of influenza in 1918 and 1927, and during the latter attack he had observed a disappearance of the livedo during the acute febrile course of the disease. Tonsillectomy had been performed in 1928 without benefit. No familial history of vascular or nervous disease was elicited. There was no previous history of thrombophlebitis or varicose veins.

Two weeks prior to admission, the patient had suffered a sudden acute pain in the right great toe which became pale and cold and remained so.

Physical Examination and Laboratory Data:

Physical examination revealed a well nourished, rather mentally depressed young man. Aside from the cutaneous manifestations, the general examination was negative. There was a marked livedo reticularis of arms, legs, and lower trunk (Fig. 1) without definite purpura or telangiectasis. A moderately deep ulcer, measuring 3 x 4 cm/. with a dirty sloughing base and slightly indurated borders, was present over the lower third of the anterior aspect of the right leg and there were several depressed pigmented scars of the skin of both ankles, and legs. The entire right great toe was pale and cold and showed a few small patches of subcutaneous hemmorhage. Pulsations in both radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial arteries were present and of normal volume. There were no postural color changes in the feet with the exception of the right first toe which became very white on elevation and excessively red on dependency. There were no varicosities. Blood pressure readings were repeatedly normal. A special tissue stain for tubercle bacilli was negative. The Kline, Kahn, Hinton, and Kolmer modification of the Wasserman test were all negative. The Mantoux test was negative. No bone or chest pathology was revealed by X-ray, and the routine blood and urine studies were all within normal limits. No lead was found in the urine. Special studies of blood smears were not significant. A small biopsy was taken from the margin of the ulcer but it showed only moderate fibrosis and a slight amount of non-specific, inflammatory reaction.

Therapy and Subsequent Course:

Since there were definite signs of a recent occlusion of the digital arteries of the right first toe, several intravenous injections of typhoid vaccine

were given with relief of pain and return of color. There was also some reason for believing that obliterative and vasospastic changes in the arterioles were the basis for both the livedo reticularis and the ulcers. Therefore, with the idea of increasing the blood supply to both toes and ulcer-bearing regions, a bilateral lumbar sympathetic galgliectomy was performed by Doctor W. Mc. K Craig on October 25, 1932. The ulcer was entirely healed within fifteen days after operation. The mottled blue areas became red below the knees and the toes and feet remained warm and dry. N o ulcers appeared for four months, the longest remission he had noted since the onset of the disease. However, at the end of that time they did recur; also, he developed an acute arterial occlusion of the left great toe similar to that previously experienced in the right, although it recovered more rapidly. Cyanosis, mottling, and sensitivity to environmental cold, of the upper extremities increased so that the patient feared that similar ulcers might develop on the hands.

He returned to the Clinic in August, 1933, complaining of new ulcers and of pains in the calves of his legs. The peripheral arterial pulsations were again entirely normal. The feet were warm (34° C.). The livedo reticularis was the same in the legs but more marked in the arms and the hands were cold, and slightly cyanotic. An arteriogram (Allen and Camp technic) of the right arm showed no evidence of arterial occlusion. Intravenous typhoid vaccine sufficient to give a systemic fever of 104° F. produced an increase of the skin temperatures of the fingers from 28.2° C. to 37.9° C.

Three roentgen ray treatments to the ulcerated areas of the legs and six subcutaneous injections of an autogenous vaccine prepared from a culture of the ulcer were also given. Partly at the patient's request and as a prophylaxis against a possible ulceration of the hands and arms, a bilateral

cervicothoracic sympathetic ganglioectomy was performed by Doctor Craig on Sept. 9, 1933, with almost complete relief of symptoms and signs in the upper extremities. During his postoperative convalescenece, the ulcers of the legs healed but whether we are justified in ascribing this to therapy other than enforced bed rest is doubtful.

The patient was discharged in October, 1933, but returned for further observation in January of the following year. In the interval between visits, he had been free of ulcers for two months only to have them return with increasingly severe pain which finally required morphine. On this admission a deep sloughing ulcer similar to the previcus ones, but larger, was present over the external malleolus of the left ankle. There was also a small area of discoloration of the ri-ht calf, which was suspected of being about to break down. A biopsy of this latter lesion showed no inflammatory reaction but some fibrosis of the corium. Two arterioles in the cutis had slight medial hypertrophy. A roentgenological examination of the leg bones showed only a slight osteoporosis. Seven daily intravaneous injections of 20 c.c. of activated suphur, six injections of the autogenous vaccine(o. 1. to 0.6 cc.) potassium iodide, and mercury by mouth were given in succession without benefit. Hot packs and pantocaine applied locally gave only slight relief from pain. Following this, during a three weeks period, five injections of 0.4 gm. of neo-arsphenamine were given without noticeable benefit. Wet dressings of potassium permanganate and thioglycerol were employed but no healing followed. The patient was even suspected of producing the ulcers and keeping them from healing and for this reason an occlusive dressing, designed so that any tampering could be detected, was applied for a period of two weeks but the ulcers became larger. Then a Balsam of Peru dressing and an Elastoplast bandage were applied with a rubber sponge for pressure overthe ulcer as advocated by

McPheeters and Merkert (8) for the treatment of stasis ulcers but no appreciable healing resulted, and the pain increased until opiates were again required. The patient became very nervous and mentally depressed and finally insisted that the left leg be amputated although he was fully aware that this was no insurance against recurrence of ulcers in the remaining leg. An amputation below the knee was finally performed by Dr. R. K. Ghormley, June 28, 1934, Convalescence was uneventful and the stump healed promptly. The patient returned home in ulceration has recurred in the right leg. There has been no noticeable progression or improvement in the livedo reticularis.

Pathologic Studies

Dissection of the anterior and posterior tibial arteries of the left leg and their vena comitis revealed no evidence of occlusion or gross pathology. However, both the long and short saphenous veins were extremely thickwalled and their lumina were very small. Histologic sections of the base and the margins of the ulcer showed considerable fibrosis of the subcortical tissue and a mild degree of inflammatory reaction. There was no evidence of any specific type of granulamatous lesion, only the appearance of chronic ischemia with low grade secondary infection of the tissues. Sections of the toes, particularly the first toe, revealed increase in the fibrous tissue, and decrease in the fat with atrophy of the cutaneous glands. The essential histologic lesions were in the blood vessels and nerves. Sections of the larger arteries such as the posterior tibial showed slight proliferation of the intima only. However, scattered throughout the tissue in the base and margins of the active ulcer and in the bases of healed ulcers and located further below the cutis than the area covered by the skin biopsies, were small arteries and veins 200 to 1000 microns in diameter which showed varying degrees

of intimal proliferation which in many cases completely obliterated the lumen. Accompanying this was a variable amount of perivascular fibrosis. In some of the arteries of the first toe, the lumen was occluded by a fibrous mass and there was marked periorterial fibrosis--apparently a late stage of the lesion. There was little or no inflammatory reaction in either the medial or adventitial coats of the small arteries and veins. The thickening of the walls of the long and short saphenous veins was almost entirely due to intimal proliferation and there was little inflammatory reaction in the vein wall itself. Many arterioles (25 to 100) microns had abnormally thick walls and small lumina; in some there seemed there seemed to be hypertrophy of the muscle and slight proliferation of the intima. In many places these were surrounded by solid fibrous tissue.

The peripheral nerves all showed perineural and intraneural fibrosis and loss of myelin sheath. This was only of slight degree in the anterior and posterior tibial nerves and their branches but was very marked in the long sphenuous and sural nerves where only a very few myelin sheaths took the Weigert stain in each nerve bundle. The vasi nervorum showed the same changes noted in other small arterioles and veins.

Comment

In summing up the essential clinical features of this case, we have a young man, aged 36, who for a period of ten years, had had a permanent livedo reticularis of the legs, arms and lower trunk, and a series of ulcers of the lower legs which gradually became more and more difficult to heal and gradually became more and more painful in spite of a wide variety of therapeutic procedures designed to increase circulation and promote healing. Finally amputation of the leg was necessary because of pain in a large ulcer which could not be healed. There were two episodes of acute arterial occlusion of toes without definite gangrene

or ulceration. There was no evidence of tuberculosis or syphilis. A lumbar sympathetic ganglionectomy seemed to inhibit the formation of the ulcers for a short time, only.

The essential pathology appeared to be proliferative, occlusive intimitis of small blood vessels, both arteries and veins, and of larger superficial veins. The term proliferative intimitis is used because both arteries and veins were affected and endarteritis and endophlebitis are loosely used in medical literature to denote a variety of vascular lesions. The arterial occlusions produced varying degrees of chronic ischemia of skinand toes and a rather marked degree of ischemic neuritis. There was also a definite thickening of the walls of the arterioles possibly secondary. There was some evidence in favor of an additional factory of venous stasis in the production of the ulcers due to the fact that veins were obstructed as well as arteries. The pathologic picture of the vascular lesions suggests that they were slow in development and distinctly different from the lesions of thromboangiitis obliterans, arteriosclerosis and periarteritis nodesa. There is no definite clue as to etiology. One would suspect that the proliferative intimitis was a reaction of the vascular endothelium to some chronic tocaemia, endogenous or exogenous. There was no evidence of syphilis, tuberculosis, or other systemic or focal infection. It is noteworthy that the patient had had an episode of clinical lead poisoning four years after the onset of the disease and it is possible that this contributed to the pathologic changes in both blood and vessels and nerves. Whether or not he had had a typical or mild chronic lead poisoning since the onset of his disease is problematical as he had had no known exposure to lead. (Subsequently, the condition was progressive over a long period when he had no contact with lead, none of the typical symptoms of lead poisoning, and excreted no lead in the urine. A specific type of vascular lesion produced by lead poisoning has never been adequately described, and possibly does not exist.) Certainly, some

viduals can have definite clinical lead poisoning without ever developing clinical or pathologic evidence of any vascular disease. However, isolated cases of several types of vascular disease have been described in association with definite clinical lead poisoning; this may be coincidental. The case described by one of us (Barker) and Brown as disseminated arteritis of unknown etiology showed proliferative intimitis of small arteries as well as arteritis and periarteritis of arterioles. There was some though inconclusive evidence for chronic lead poisoning in this case in that lead was found in the urine during life and in certain tissues of necropsy.

One remarkable aspect of the case herein reported was its slow but definite progression and refractiveness to therapy. On this basis, the prognosis, both as to loss of other limb and life is uncertain.