ANGIITIS WITH NODULE FORMATION, VASOMOTOR INSTABILITY AND SECONDARY CUTIS LAXA*

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Suggesting the existence of a new syndrome is always perilous, for the biblical axiom "there is no new thing under the sun" often holds in clinical medicine. Yet when a group of symptoms and manifestations, never before observed in such combination, occur in one particular patient repeatedly and with increasing severity during a period of more than ten years, the possibility that it constitutes a unique syndrome is worth considering. A detailed study of this puzzling case, therefore, is presented.

REPORT OF CASE

History

In 1947, D. D., a 37-year-old woman, began to suffer attacks of pain in the knees. The attacks were more intense before the menstrual period, when she was "nervous," or after she had been chilled. In 1949 acute attacks of edema of the hands and feet, during which the skin became so tight that it would "break" began to occur. These periodic swellings also were related to the menstrual cycle, being initiated by pain in the joints about ten days prior to menstruation. In addition to the pain, a feeling of stiffness in all joints developed. As the intermittent attacks of edema continued, the hands and feet became progressively enlarged with the result that during remissions of the edema the skin was loose and wrinkled. Attacks of edema involving the knees, scalp, face, and buttocks also appeared; occasionally, circumscribed, red and tender swellings, measuring 10 cm. in diameter, on the wrists and legs lasted for three or four weeks at a time.

The feet then became subject to attacks of such intense hyperhidrosis that shoes could no longer be worn since they would become soaking wet within a short period. For this reason bilateral lumbar sympathectomy was done in 1952 which was followed by elimination of the excessive perspiration, although the pain continued. The edema of the feet became constant and even aggravated; the patient feels that at present her feet are about 50 per cent larger than they were before the sympathectomy.

For some time now the edema of the fingers and the toes has been constant. "Giant hives" also occur intermittently and can be precipitated by trauma. During the last few years the skin of the elbows, fingers, and toes has become inelastic. She was examined, at one time, by a renowned vascular surgeon in Strassbourg, France, who told her she had Ehlers-Danlos disease. Another development of late is the intermittent appearance of "kernels" which can be felt under the skin of the balls of the fingers and on the elbows and the ears; the nodules of the ears occasionally become ulcerated.

In 1952 the patient received shock therapy for an unspecified emotional disturbance.

The family history reveals that one sister also has attacks of edema which are not, however, so severe as those of the patient. The sister is said to be "highly nervous" and her attacks of swelling are said to be precipitated by emotional tension.

Physical Examination

The patient is a small woman, 63.5 inches (161.3 cm.) tall, weighing 109 lbs. (49.4 Kg.). Her temperature, pulse, respiration, ophthalmoscopic findings, thyroid, heart, lungs, and abdomen are all normal. Her blood pressure is 112 diastolic, 72 systolic. There is normal pulsation of all of the peripheral arteries. There is no palpable lymphadenopathy in the axillary or femoral regions. The bony structures are not enlarged.

The skin of the fingers, toes, and elbows is cyanotic and so loosely attached to the under-

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Robert R. Commons, M.D., University of Southern California School of Medicine performed the endocrine survey.

Youssef K. Mawardi, M.D., gave the patient psychotherapy over a period of two years.

lying structures that it hangs in baggy folds, especially at the elbows and on the balls of the fingers. The fingers are club-shaped. Firm nodules 1 to 3 mm. in diameter can be felt at times under the skin of the fingertips and on the ears. On one occasion there was a localized swelling on the right forearm (Figs. 1–7). The nails of both hands and feet are dry, transversely ridged, and break easily.

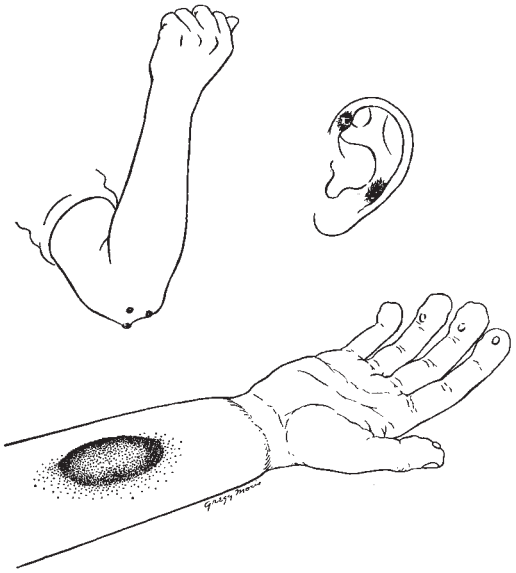

FIG. 1. Nodules of fingertips, concha, and elbow; circumscribed swelling on forearm.

In addition to the abnormal wrinkling of the skin of the feet, there are dried vesicles on the soles. Fungi were demonstrated microscopically, and *Trichophyton mentagrophytes* (gypseum) was grown on culture.

An erythrocyte count was 5.07 million with 14.7 Gm. (105%) hemoglobin. The platelet count was 188,000. The sedimentation rate was 13 mm. in one hour, and the hematocrit 45. Coagulation time was 7 minutes. The leukocyte count was 6,300 with 16% segmented and 6% nonsegmented neutrophils, 30% lymphocytes, 1% monocytes, and 2% eosinophils. Blood urea nitrogen was 31 mg. per hundred cc., blood sugar 97 mg., blood chlorides 366 mg., blood cholesterol 325 mg., blood calcium 9.1 mg. Serologic test for syphilis (Kline) was negative. Study of blood for presence of "L-E" cells of Hargraves was negative (lupus erythematosus). Cold agglutinins were within normal limits (1,16); cold hemolysins and cryoglobulins were absent.

The urine volume was 2,600 cc., creatine 0.78 mg., and 11-oxysteroids 0.64 mg. in 24 hours. Specific gravity was 1.029, reaction pH 6; examinations for albumin, sugar, casts, red blood cells and white blood cells were negative.

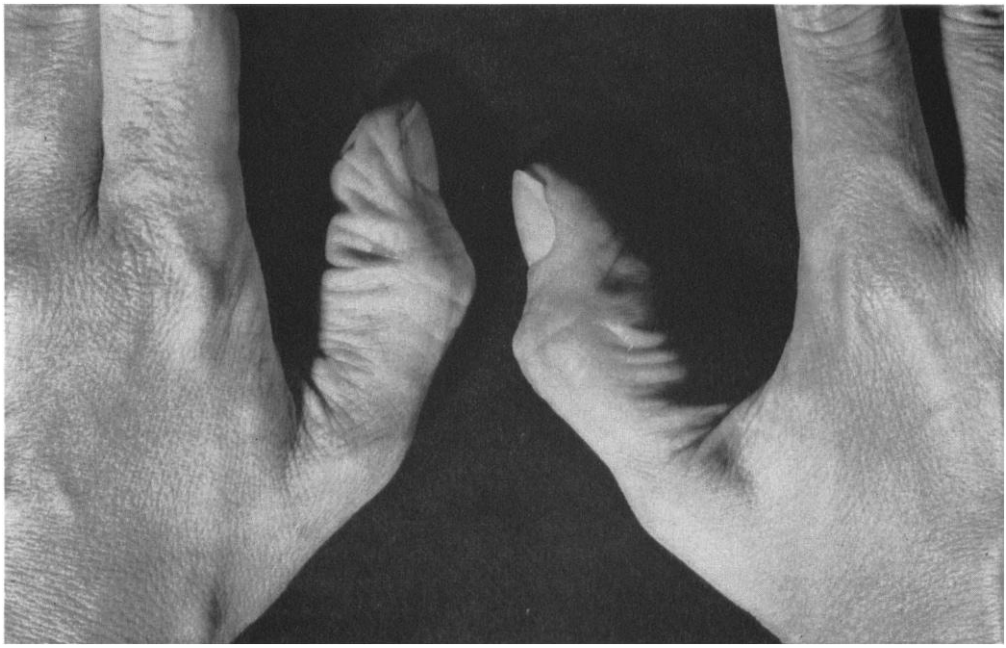

FIG. 2. Cutis laxa of thumbs.

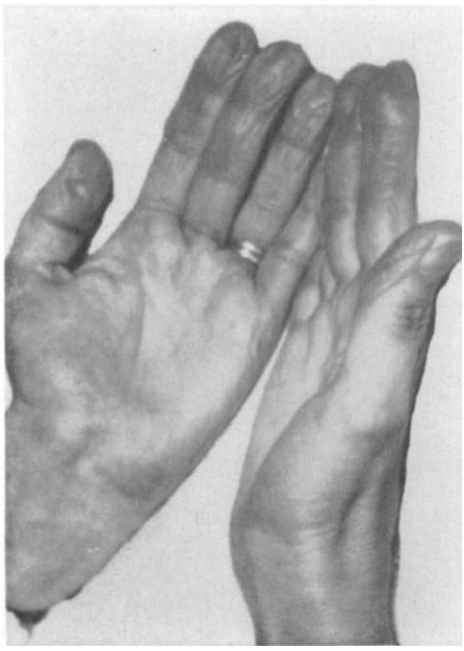

FIG. 3. Cyanosis, cutis laxa, and nodules of fingertips.

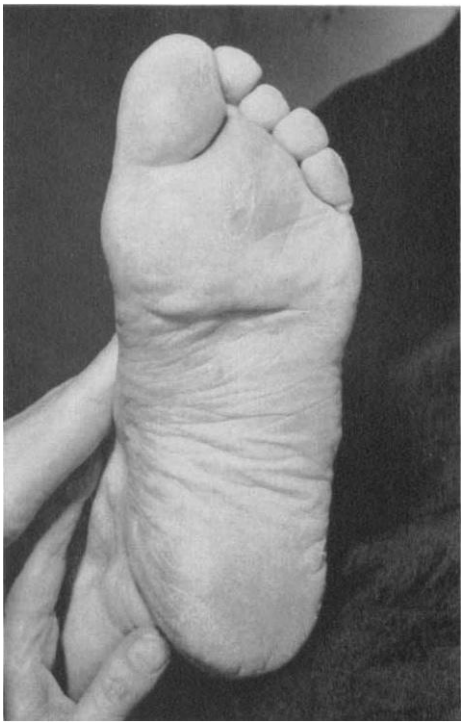

FIG. 4. Abnormal wrinkling of sole, edema of toes, ulcer in process of repair over point of pressure.

An electrocardiogram revealed no abnormality. The heart and lungs appeared normal on a roentgenogram of the chest. Roentgenologic study of the joints did not disclose any bony abnormalities.

Vascular Reactions

The vascular reactions were studied extensively and some of the observations were as follows:

Capillaries of the Nail Bed. The patient's circulation was observed on two occasions during the cold cyanotic stage and during the hot, red, painful stage. During the cold stage the capillary loops were greatly dilated and the venous limbs were constricted, the loops being similar to those seen during the constricted stage of Raynaud's phenomenon, and the blood flow was exceedingly slow and granular. During the hot stage the capillaries were considerably less dilated and the blood flow was rapid and less granular.

Reactions of Blood Vessels of Fingers and Toes to Alcohol and Heat. A sharp increase in cutaneous temperature occurred. The hand changed from cyanotic to pink with a rapid appearance of swelling of the fingers.

Tests for Postural Hypotension. The patient was required to stand in the upright position for five minutes without moving. At the end of this time she became pulseless and fainted; she was unconscious for 30 seconds.

Posture Test. One hand was allowed to remain down by the patient's side and the other hand was elevated for five minutes. The hands were then brought to heart level and observed. There was marked swelling of the fingers of the hand which had been down; the skin of the fingers was tense, shiny, and cynotic. The fingertips of the hand which had been raised were pinched, with loose, wrinkled, less cyanotic skin. The difference in volume of the fingers of the hand that had been raised compared with the volume of the fingers of the hand permitted to hang down was 63 per cent. This difference varies from 8 to 20 per cent in normal subjects (Fig. 8).

Digital Plethysmogram. Unusually large fluctuations in the amplitude of pulsations of the digit occurred. (Fig. 9). Recordings were made with a digital pneumoplethysmograph with the patient supine in a comfortable, warm environment and with the hands elevated twelve inches above the

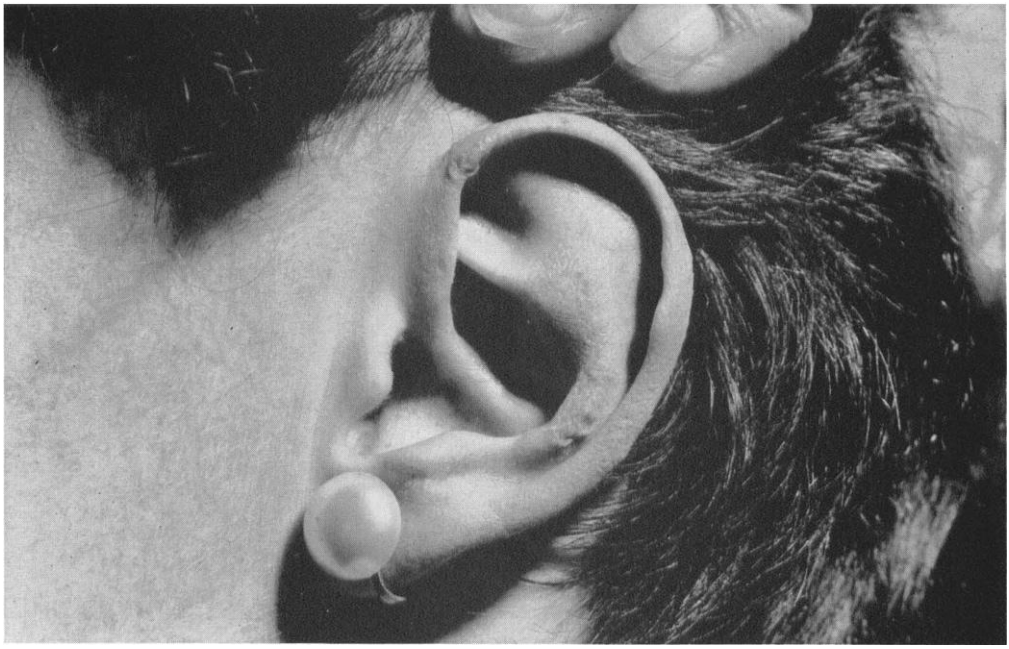

FIG. 5. Ulcerated nodules of ear.

level of the heart. Records were made continuously over a period of five minutes. At times the amplitudes of pulsation greatly exceeded those of normal control subjects. After a few seconds of excessive vasodilatation there followed marked vasoconstriction during which time the pulse waves became small and they were absent for many seconds. These rapid fluctuations with extremes of vasoconstriction and vasodilatation continued rhythmically approximately twice per minute during the observation.

Relationship of Cutaneous Temperatures to Symptoms. When the cutaneous temperature of the fingers was warm, that is greater than 32 degrees C., there was swelling and pain. When the fingers were cool, pain was slight or absent. It is of interest that, since the time of the sympathectomy, the cutaneous temperature of the toes has been almost always warm, yet there is persistent pain in the toes.

Elevation of the foot decreased the pain, but would not halt an attack of swelling once it had started. Wearing of sandals was more comfortable than wearing closed shoes. Placing the hands in cool water (6 degrees C.) produced temporary

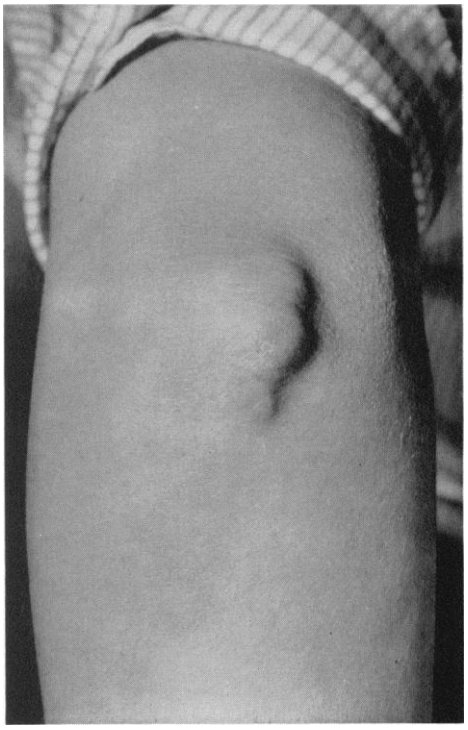

FIG. 6. Nodular stage of elbow.

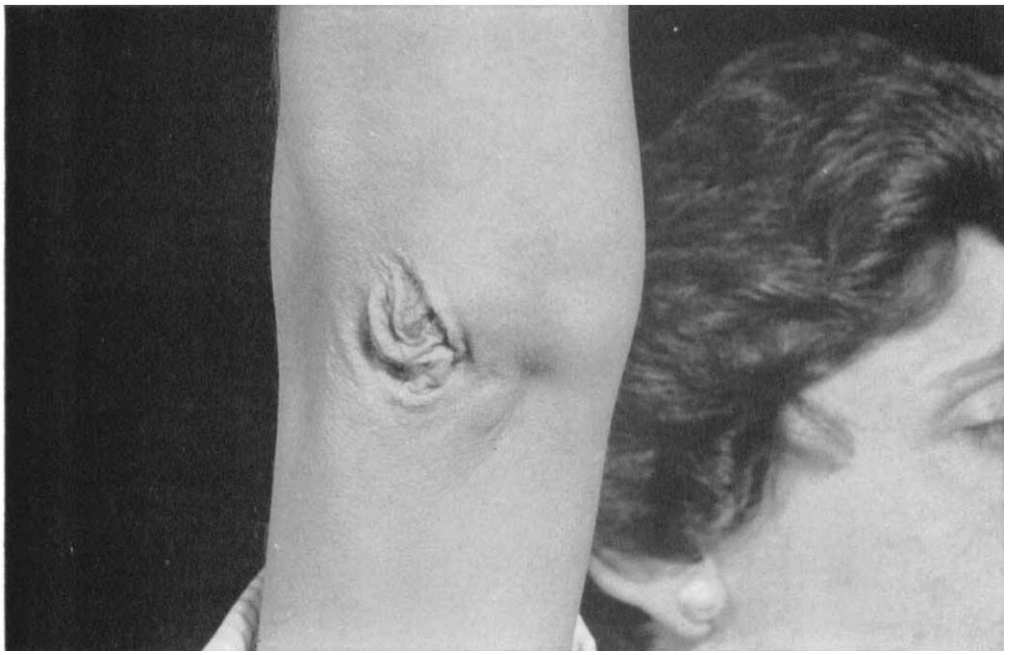

FIG. 7. Cutis laxa stage of elbow.

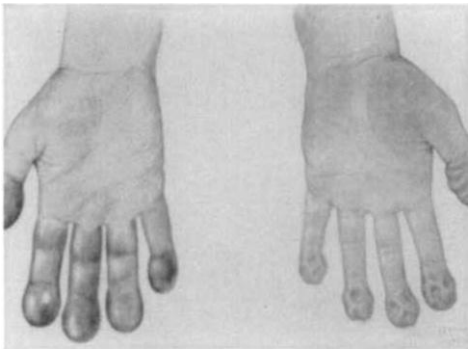

FIG. 8. Posture Test. Hand on left had been down by patient's side, and demonstrates characteristic swelling of fingertips and cyanosis. Hand on right had been elevated, and demonstrates characteristic wrinkling of skin of fingertips and less cyanosis.

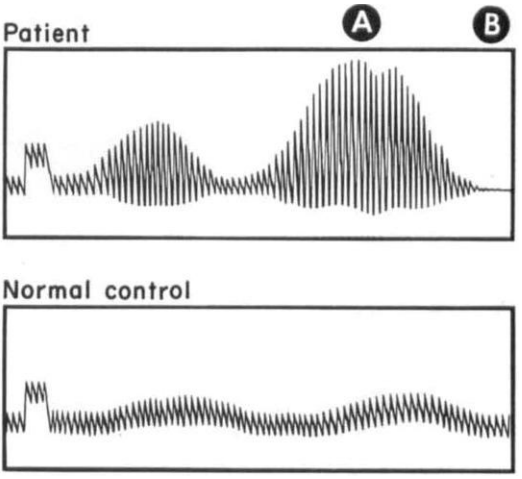

FIG. 9. Digital Plethysmogram. A indicates abnormally large amplitude of pulse. B indicates almost complete cessation of pulsation.

relief of pain, but on removing them from the water the burning pain would return.

The situations that aggravated the patient's symptoms were putting of her hands in hot water, trauma such as opening cans or turning on the water faucet, venous obstruction, the weight of bed clothes on her feet, the wearing of tight shoes, heat from the motor of her car on the bottom of her feet, exercise which produced swelling of the hands and feet, dependency of the hands and feet which aggravated the swelling, nervous tension, eating of heavy meals which precipitated attacks, exposure to the sun which produced pain and edema, and warm weather which increased the number of attacks.

Histopathology

Since it was felt that the best clue to the nature of the disease might be found by examination of the nodules, two biopsy studies were performed, one from the ball of one finger (January 1957) and one from the left elbow (November 1957). The histologic picture of the sections from both specimens was essentially the same, except for an acute suppurative reaction in the nodule of the finger which reaction involved all layers of the dermis, a feature only developed to a minor extent in the nodule from the elbow. Therefore the following description applies to the nodule from the elbow.

The epidermis is essentially normal with only slight hyperkeratosis. There is an active inflammatory reaction of the dermis in relation to the arterioles and to the capillaries, and also to several tiny arteries. This process is present in all layers of the dermis, and the perivascular infiltrate is composed predominantly of polymorphonuclear leukocytes and mononuclear cells, and in addition an increased number of eosinophils and a lesser of histiocytes. In many of the leukocytes there is evidence of karyorrhexis. In a few sites nuclear debris is present within the cytoplasm of macrophages. The infiltrate invades the vessel walls and there are varying degrees of endothelial proliferation leading to vascular occlusion. Several arterioles and capillaries present concentrically arranged spindle and polygonal cells around their walls; these cells, which are several layers in thickness, appear to be histiocytes and fibrocytes. In places the perivascular cellular pattern appears epithelioid, but there are no tuberculoid granulomas. The entire picture is that of an acute, necrotizing and obliterative angiitis involving capillaries and venules, arterioles and small arteries (Figs. 10 and 11). The microscopic sections were also examined by a number of experts whose opinions will be discussed under the headings Comments.

Endocrinologic Survey

Measurements of the function of individual glands did not reveal any abnormalities, but the endocrine system as a whole was found to be unstable with wide fluctuations in levels. Attempts to suppress the function of the patient's own endocrine organs by means of high doses of thyroid, estrogen, and prednisolone were followed by improvements in the symptomatic picture.

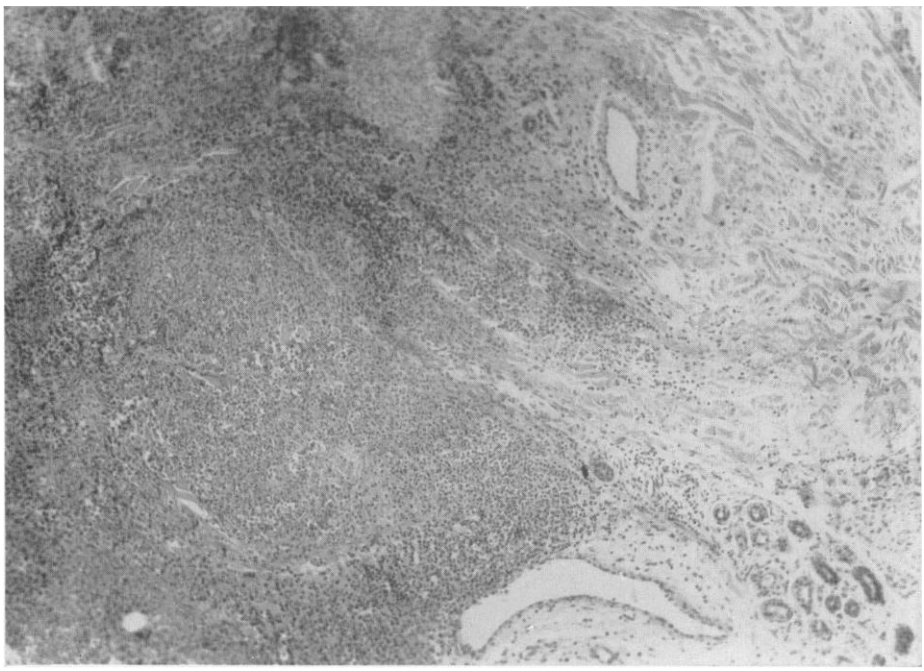

FIG. 10. Microphotograph of section from nodule of elbow (50 ×) demonstrating dermal cellular infiltrate.

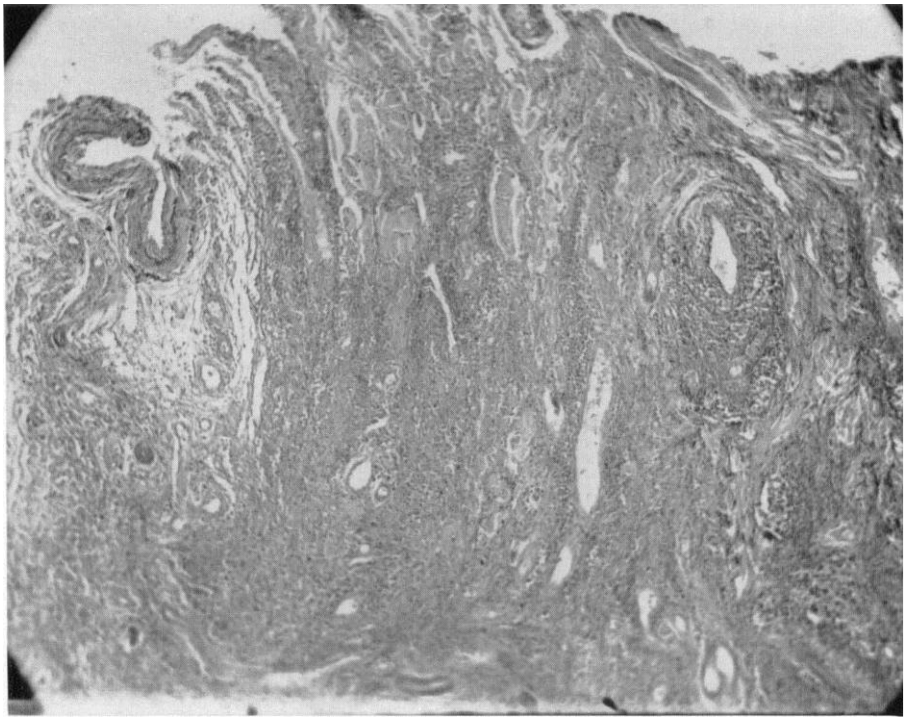

FIG. 11. Microphotograph of section from nodule of elbow (40 ×) demonstrating inflammatory changes in relation to blood vessels.

Psychiatric Survey

The initial complaints of the patient were constant fatigue brought about by excessive nervousness associated with agitation and lack of sleep, suggesting an agitated depression. In the course of psychotherapy it became apparent that the emotional disorder was an obsessive-compulsive reaction in a fundamentally schizoid personality.

Treatment

Treatment has consisted in administration of practically all drugs employed in the therapy of peripheral vascular disease. The steroid hormones have also been used. A variety of sedatives were tried and of these (mepazine) Pacatal® was most helpful; it is of interest that this drug interferes with conditioned vasomotor responses (1, 2). Dibenzyline which is reported to bring about improvement in Weir-Mitchell's disease was ineffective. Acetylsalicylic acid had only a mild analgesic effect. Antihistamines in large doses decreased the swelling to a slight degree. A large number of vasodilators, vasoconstrictors, and anticholinergic drugs were tried but to no avail, although some benefit seemed to be derived from ephedrine. Numerous anticapillary fragility drugs likewise were nonefficacious. The most effective therapy was administration of prednisolone, thyroid, and estrogens given to prevent large fluctuations in endocrine activity. The stiffness of the joints was relieved by prednisolone and combined endocrine therapy.

COMMENT

It is obvious that this is a disease in which vasomotor disturbance and acute recurring angiitis are prominent features. To establish the unique nature of the syndrome it is necessary to differentiate it from other diseases in which these features are operative and determine if any such diseases may at times be accompanied by the bizarre symptoms exhibited in this patient.

The disease that most closely resembles that in our patient is erythromelalgia which was first described by Mitchell in 1878 (3), and later by Smith and Allen (4) under the name of erythermalgia to denote the common association of redness, pain, and increased temperature of the affected parts. While there are many similarities, there are also important differences. In our

patient, headache, vertigo, and palpitation are lacking, while the nodules of acute angiitis, involvement of the joints, and the relationship to the menstrual period are not features of erythermalgia.

Other differential diagnostic conjectures, motivated primarily by the histopathologic findings, concern periarteritis nodosa, erythema elevatum diutinum, the leukoklastic microbic Id of Miescher, and allergic angiitis.

Periarteriitis nodosa does not have features of vasomotor disturbance, although, as Montgomery (5) commented on first viewing the sections in our case, the process in the nodules may—if the term periarteriitis nodosa is used in a larger sense—be called possibly a modified form of periarteriitis nodosa limited to the skin. The histologic appearance of the section of the nodule from the finger is compatible with the diagnosis of erythema elevatum diutinum, according to Becker (6), but this term has little meaning since the entity it represents is regarded today as but a form of allergic angiitis. The leukoklastic microbic Id of Miescher (7), with which our microscopic picture is also compatible, is another form of allergic angiitis thought to be due to a focus of infection. Miescher (8) said that the histologic changes demonstrated in one of our sections indicate that the disease could very well be leukoklastic microbic id. Hypersensitivity angiitis as defined by Zeek (9) probably fits the nodular process in our patient and this opinion is shared by Bangle (10) and also by Montgomery (5). In fact the nodules seem to be analogous to "Osler's nodes" noted on the volar aspects of the distal phalanges in patients with subacute bacterial endocarditis which also constitute angiitis with obliterative changes. "Osler's nodes" are caused by septic emboli of known bacterial origin. The parallel to Miescher's leukoklastic microbic id is obvious.

Thus all diagnostic considerations based on the biopsy point toward a form of allergic angiitis. But this is only part of the picture and offers no explanation for the great variety of symptoms exhibited in our patient.

The diagnosis of Ehlers-Danlos disease, which was made by a specialist in peripheral vascular disease in Strassbourg, France, and again suggested by Parry when the patient was presented before the Los Angeles Dermatological Society (January 9, 1957) (11) is not supported by the available evidence. The cutaneous changes on the elbows and fingers lack the feature of hyperelasticity which is characteristic of Ehlers-Danlos disease. They represent merely cutis laxa, a stretching and loosening of the skin which, in our patient, was brought about by the tremendous changes in volume of the parts during the attacks of edema.

For an explanation of the dominant symptoms in this patient a disturbance of the whole vascular regulatory mechanism must be assumed. The contradictory behavior of the peripheral vascular system as demonstrated by the posture test is illustrative. The angioneurotic edema, the features of Raynaud's disease, and the erythermalgia are only parts of our patient's syndrome.

It is difficult to state how much of a causal role the psyche has in this patient. Psychiatric survey established that she is an emotionally disturbed person. The intermittent nature of her complaint is suggestive: While she was on a trip to Europe two years ago the manifestations were minimal but immediately on return to her local environment they again became severe. We are wondering whether this patient's symptoms are not identical to those described by Feré, in 1897, as occurring in hysterical women of the period. (12).

The idea that a focus of infection might be responsible for the allergic angiitis as well as for the disturbance of the vascular regulatory mechanism is not illogical. But no such focus could be demonstrated. Nor could the disturbance be ascribed to any organic change in the central nervous system. Yet the symptoms point toward a disturbance in the vasomotor center and this view is further supported by the elimination of the edematous attacks on the feet through the bilateral lumbar sympathectomy. The persistent swelling of the feet following this operation may be explained as the result of permanent capillary damage due to the numerous episodes of swelling preceding the sympathectomy.

One may speculate on the possibility of a physical allergy acting on the vasomotor center, the attacks of which are precipitated by a variety of situations ranging from changes in temperature, exposure to heat, or physical trauma to emotional tension.

SUMMARY

A patient exhibiting a syndrome consisting of hypersensitivity angiitis with nodule formation,

various striking features of vasomotor instability, and secondary cutix laxa was studied in detail. It is concluded tentatively that these phenomena are the consequences of a disturbance in the vasomotor center produced by physical allergy.

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