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LOCALIZED SUBCUTANEOUS OEDEMA WITH WEAKNESS OF LIMB MUSCLES A SYNDROME DUE TO POLYARTERITIS NODOSA

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The three cases of polyarteritis nodosa described here are of interest for several reasons. They all showed as the two salient features a localized soft pitting oedema of the skin of one or more limbs together with asymmetrical muscular weakness—a clinical picture not previously described. Two of these patients recovered from the illness. All three cases were diagnosed in life, the diagnosis being confirmed by biopsy. The three cases were seen in one hospital in a period of 18 months, which suggests that Leishman (1937) was right in suggesting that this disease, though very varied in its forms, should be recognized more frequently. It may be observed that during this period, although polyarteritis was being looked for, in only one other case was it suspected, and this showed a clinical picture very similar to that of the three cases. The biopsies, however, were negative.

Case I (an Engineer aged 27)

The family history was irrelevant. There was a previous history of a cough for 12 months and of a coryza towards the end of April, 1940. On May 1, 1940, while at work, the patient injured his right calf and had to take to bed. Two days later, while in bed, he found that he had great difficulty in moving the right thigh—attempts causing pain in the groin—and that he was unable to lift his right forearm off the bed or to raise the arm at the shoulder.

On May 6, 1940, he was admitted to St. James Hospital, London. He was of slim build and in fair general condition; his temperature was 99.6° F., the pulse rate 88, and the respiration rate 24. No abnormal signs were found in mouth, lungs, heart, or abdomen; his blood pressure was 135/85 (a week later it was 120/80). A mild degree of clubbing of the finger-nails was present. There was considerable weakness of the right deltoid and biceps muscles, which were tender on palpation. The right upper arm was swollen—the circumference being 9½ in., against 8 in. on the left side—from diffuse soft pitting oedema. The skin was not inflamed. There was no sensory loss or any paraesthesiae at this time or later. The muscles of the right thigh were weak and tender, and pain was felt on externally rotating the flexed thigh. There were two subcutaneous nodules on the outer side of the right calf, but no oedema there. The left arm and leg were normal. The patient was treated by rest in bed and a high vitamin diet (with bemax, cod-liver oil, ascorbic acid, and iron), and massage at a later stage.

Investigation on Admission.—Urine, nothing abnormal. Blood urea, 36 mg. per 100 c.cm. Blood count: R.B.C. 5.5 millions; Hb 92% (Haldane); platelets normal; W.B.C. 12,000—neutrophils 79%, lymphocytes 15%, monocytes 6%. (Nine days later: Hb 97%, W.B.C. 12,000, neutrophils 69%.) Sedimentation rate, normal. Sputum: no tubercle bacilli on 3 examinations; culture pneumococci. Radiograph of chest (May 13, 1940): Increased markings at both hila, and a small amount of fluid or thickened pleura at the left base. (A further chest radiograph two weeks later showed no change.) A radiograph of the right upper arm revealed no abnormality. Cerebrospinal fluid: Clear, colourless, 2 cells per c.mm.;

protein, 40 mg.; globulin nil; chlorides, 740 mg.; W.R. and Lange negative. Blood W.R. and K.R. negative. An electrocardiogram on May 26 showed poor T-waves and slight elevation of ST, with depression of ST. These changes were still present 10 days later.

Progress in Hospital.—For 2½ weeks he had a symptomless pyrexia and a rather longer-lasting tachycardia (Fig. 1). The swelling of

FIG. 1.—Temperature and pulse chart of Case I.

the right arm had increased the day after admission to 10½ in. circumference, but in a few days it began to diminish and in two weeks it was gone. The weakness of the right arm and shoulder persisted for 10 days before improving, but had cleared up in 4 weeks. A week after admission there was still tenderness at the insertion of the biceps muscle, and some pain was felt on using the triceps. There was also a tender nodule, about 0.5 cm. in diameter, beside the brachial artery at the level of the biceps tendon. The power of the right thigh improved from the time of admission. A week after admission one small tender subcutaneous nodule was observed on the outer side of the right calf, and also an erythema-nodosum-like lesion of the skin over the shin. On May 11 he complained of pain in the left orbit, but no lesion or oedema was seen. The patient started getting up on June 3, and for a few days after this the dorsum of the right foot showed a little soft oedema. There was no tenderness or weakness of muscles of the legs, and the ankle-jerks were present though not brisk. On June 9, five weeks after admission, he left the hospital quite well.

On May 22 a biopsy specimen was taken of a nodule, 0.3 cm. in diameter, attached to a small subcutaneous vessel in the right arm. The histological report was: "Polyarteritis nodosa in nodule from subcutaneous tissue of arm."

Two and a half years later, in Oct., 1942, he and his private doctor both reported that he had remained perfectly well.

Case II (a House-painter aged 63)

This man had had a chronic cough for many years. He took alcoholic drinks in moderation only. On Nov. 5, 1940, he developed a "numbing pain" in the lumbar region and shoulders radiating down the arms. There was no weakness of the limbs. Two days later his ankles began to swell and he became short of breath. On Nov. 11 he was admitted to St. James Hospital.

On admission his general condition was fair. His temperature was 97.6° F., pulse 84 regular, and respirations 20. The heart was normal in size and sounds; the brachial arteries were thickened. There was soft pitting oedema ++ of the ankles, but nothing else to suggest congestive heart failure. He was not orthopnoeic. The lungs showed signs of diffuse bronchitis, but there was little sputum and no haemoptysis.

Investigations on Admission.—The urine was normal. There were moderate anaemia and a leucocytosis (R.B.C. 3.5 millions, Hb 77%; W.B.C. 15,200—neutrophils 85%, eosinophils 1%, lymphocytes 11%, monocytes 3%). The blood W.R., K.R., and gonococcal complement-fixation test were negative. The blood sedimentation rate was very rapid—53 mm. on 100 mm. column at 1 hour. The sputum showed no tubercle bacilli; one culture yielded a fair growth of Friedländer's bacillus. An x-ray film of the chest showed only the increase in vascular markings common in chronic bronchitis. Radiographs of the limbs revealed no abnormality in bones or joints. The blood urea six weeks after admission was 60 mg. per 100 c.cm., and

FIG. 2.—Case II. Photomicrograph showing necrosis of arterial wall. Stained haematoxylin-eosin. ($\times 95$.)

the plasma protein at this time showed a great rise in albumin. Total protein, 9.9% (normal 5.6 to 7.8%); albumin 7.55% (normal 3.4 to 4.9%); globulin 2.35% (normal 1.2 to 2.9%).

The patient was treated by rest in bed, with bexam, iron, and theophylline by mouth and simple analgesics for the pains.

Progress in Hospital.—Four days after admission he developed pain in the legs. The calf muscles were tender and movements of the ankle-joints were painful and weak. The ankle-jerks were absent, the knee-jerks faint, the plantar responses flexor, and the abdominal reflexes present. There was no pain or oedema in the upper limbs at this stage, but the triceps-jerks were absent. No inflammation of the skin or any nodules were present at this or any later stage.

Though the oedema of the feet persisted, the pain in the legs cleared up in a week; but before it had gone pain developed at both elbows. On Nov. 17 neither elbow could be fully extended; the right ulnar nerve was tender but not the left. In contrast there was pitting oedema of the dependent skin at the left elbow, but none on the right. There was also tenderness deep in the right antecubital fossa. A blood count at this time showed no leucocytosis (W.B.C. 6,200), though the B.S.R. was still very rapid—48 mm. at 1 hour. On Nov. 23 pain and soft pitting oedema had appeared at the back of the left thigh, and the pain at the left elbow was worse.

On Nov. 27 the patient complained of paraesthesiae in the right hand; but the legs and arms were much more comfortable, and the swelling at the left elbow began to diminish. A week later, however, he had a severe pain in the left forearm, with tinglings in the left hand, diffuse swelling of the left forearm, and weakness of the

left wrist and hand. On the right side there was now no weakness or pain.

On Dec. 6 and 7 he complained of a "different sort of pain" in the abdomen. There was tenderness at the renal angles, and the urine, previously normal, contained albumin, with many red cells and a few leucocytes in the deposit. Some albumin and blood were present in the urine every day from this time till his death five weeks later; and in the last three weeks of his life there were increasing numbers of granular casts. On Dec. 6 it was observed that a mild clubbing of the finger-nails had developed since his admission.

On Dec. 9 he had a severe pain in the left leg and tenderness in the lateral part of the left popliteal fossa, but no fresh oedema. A week later he was becoming drowsy and losing ground. There was now oedema of the ankles, the back of the left thigh, and the left upper arm. The blood count on Dec. 17 showed Hb 72%, W.B.C. 15,600 (neutrophils 80%, eosinophils 5%). He was given a transfusion of a pint of citrated blood, and two days later the blood count was Hb 80%, W.B.C. 15,600 (neutrophils 84%, eosinophils 4%).

He was now (Dec. 19) complaining of severe pain, and the oedema was present in the right thigh as well as the left, and there was a manifest left wrist-drop. He was started on injections of vitamin B₁,

FIG. 3.—Case II. Photomicrograph showing polymorph infiltration in vessel wall. Stained haematoxylin-eosin. ($\times 140$.)

2 mg. on alternate days. On Dec. 24 he was definitely better, with less pain and oedema but some mild paraesthesiae of the hands and feet. The knee, ankle, triceps, and supinator jerks were absent, and the responses from the biceps were faint. The blood pressure was 150/110; there were no signs of congestive heart failure.

The anaemia and leucocytosis were both increasing (Hb 66%; W.B.C. 22,000, neutrophils 97%, on Jan. 3, 1941). He became steadily weaker, his face getting thinner, with an earthy pallor. Oedema now appeared in the right as well as the left arm and increased, and in the legs it became generalized. A course of sulphapyridine was without any good effect. He died on Jan. 12, 1941.

The biopsy report on material taken on Dec. 9, 1940, from subcutaneous tissues and flexor muscles of the left arm was: "Polyarteritis nodosa. Hyaline necrosis of wall of small artery with surrounding acute purulent inflammatory reaction." (Figs. 2 and 3.)

Necropsy.—A necropsy was made the day after death. The bronchi contained much muco-pus and were somewhat dilated at their terminations. Both lower lobes showed diffuse bronchopneumonia. The heart muscle appeared quite normal. There were lines of redness along the descending branches of the right coronary artery, but no nodules or aneurysms. Atheromatous patches were present in both coronary arteries and in the aorta. No nodules were seen on the mesenteric vessels. The liver showed only slight venous congestion. Both kidneys had a smooth surface mottled from many

cortical infarcts. On section the cortex was of normal width; there were two small circular areas suggestive of aneurysm.

Histological Report.—The kidneys showed diffuse chronic nephritis and focal ischaemic nephritis, and also severe chronic purulent inflammation and necrosis of arcuate arteries, some with canalized organized thrombosis. Aneurysmal dilatation of an artery and a purulent infarct of the cortex were also seen. There was chronic purulent inflammation and necrosis of coronary arteries of the heart and of arteries in the mesentery. Tissue from the axilla showed chronic purulent inflammation of the axillary artery and of its branches in adherent nerve and muscle. Changes in other organs were bronchopneumonia, chronic septic spleen, congestion of the liver, and fibrosis of the myocardium.

Case III (an Escalator Engineer aged 58)

This patient had a history of recurrent coughs. He took no alcoholic drinks. About August 10, 1941, he developed aches and pains all over and a dull pain at the navel. There were night sweats, and he noticed that he was passing less urine. He had an occipital headache, poor vision and weeping eyes, and some attacks of faintness. His appetite remained good. A week after the onset of these symptoms he began suddenly to have numbness and tinglings and weakness of the hands, progressing to uselessness, and similar paraesthesiae and a slighter degree of weakness of the legs and feet. Two weeks after the illness began the left side of his face became puffy and the ankles swelled. He was admitted to St. James Hospital on Sept. 1, 1941.

He was in fair general condition, of sallow complexion; temperature 98°, pulse regular 76, vessel not thickened; respirations rapid (44) but not distressed. The heart size and sounds were normal. There was no orthopnoea; the lungs were clear. There was no venous engorgement or hepatic enlargement; his blood pressure was

peripheral neuritis. The patient was treated by rest in bed with a high vitamin diet. He was given aneurin 10 mg. by intramuscular injection daily for four days, and splints and physiotherapy for the limbs.

Investigations.—Circulation times (Sept. 12) normal (ether 8 and 10 seconds; cyanide 15 and 15 seconds). An x-ray film of the chest showed no evidence of disease of the lungs, heart, or mediastinum. Blood W.R. and K.R., negative. Blood urea variable—70 mg. per 100 c.cm. (Sept. 4), 36 mg. (Sept. 16), 70 mg. (Sept. 23). Plasma proteins (Sept. 16) were very high from excessive amount of albumin (total 8.45%—albumin 5.9, globulin 2.55; albumin/globulin ratio 2.3 : 1 (normal values: total 5.6–7.8%; albumin 3.4–4.9, globulin 1.2–2.9; albumin/globulin ratio 2–3 : 1). A blood count on admission (Sept. 2) showed anaemia and a neutrophil leucocytosis. (R.B.C. 4.3 millions, Hb 68%, C.I. 0.8; group O; W.B.C. 9,800—neutrophils 84%, eosinophils 4%, lymphocytes 10%, monocytes 2%.) Serum salts (Sept. 23): chloride 580 mg., potassium 14.5 mg., sodium 324 mg. (normal values: 560–620, 16–20, 325–350).

Progress in Hospital.—During his 3½ months in hospital the patient's temperature was often raised (Fig. 4). A course of sulphathiazole started on Sept. 13 had no effect. The blood pressure—200/110 on admission and 225/135 two days later—gradually fell to 160/90 (Oct. 23). The abnormal urinary constituents gradually diminished to a little albumin with a few red cells in the deposits. The oedema varied but never disappeared. There were never any signs of heart failure, right- or left-sided. The pain in the limbs varied; at one time he complained of shooting pains, but chiefly of the numbness and progressive weakness of the hands. The anaemia increased; three weeks after admission the Hb was 48%, with W.B.C. 7,200 (neutrophils 79%, eosinophils 7%).

On Oct. 1, a month after admission, he developed diarrhoea. The stools contained no mucus, blood, parasites, or pathogenic organisms.

FIG. 4.—Temperature chart of Case III.

200/110. Slight tenderness was felt in the loins. The urine contained much albumin, the deposit showing many red cells, a few leucocytes, and some hyaline casts; no organisms were seen or grown on culture. There was much soft pitting oedema of the upper limbs, especially in the dependent part of the forearms and near the elbows; this was more extensive on the right side. There was also soft oedema behind the ankles, especially on the left. The face was free of oedema.

Examination of the nervous system revealed no defect of the cranial nerves. Both deltoids showed some weakness. On the right side there was slight power of flexion of the fingers but complete wrist- and finger-drop, and flexion and extension of the elbow were weak. On the left side he could not oppose the thumb and fourth finger, but flexion and extension of fingers and of wrist were good; there was fair power of flexion of the elbow but considerable weakness of extension. The lower limbs showed slight general weakness. The right triceps, biceps, and supinator jerks were absent, while on the left they were respectively sluggish, normal, and sluggish. The left knee-jerk was brisker than the right; the ankle-jerks were both sluggish. The plantar responses were flexor, the lower abdominal reflexes absent, and the upper normal.

The electrical reactions of the muscles were tested. In the left upper limb these were normal. On the right all muscles reacted to galvanism; to faradism the triceps and extensor muscles of wrist and fingers did not react; the deltoid and biceps reacted weakly; and the muscles of the flexor aspect of the forearm and the intrinsic muscles of the hand reacted normally.

There was on the right a gross loss of sensation of the hand and lower part of the forearm; and on the left, of the hand only. The legs showed diminished sensibility to light touch, of stocking distribution. Position and vibration sense were good. There was no tenderness of the muscles of the upper or lower limbs.

The combination of an asymmetrical polyneuropathy with oedema suggested the probability of polyarteritis nodosa. Dr. E. A. Blake Pritchard saw the case; he thought it was not a syndrome due to

Per rectum several small submucous nodules could be felt. Sigmoidoscopy showed a normal mucosa. By the middle of October there was much soft oedema in the lumbar region as well as in the elbow regions and at the ankles. The muscular weakness had increased in the left wrist, in both arms, and in the dorsiflexors of the ankles. There was marked wasting of the intrinsic muscles of the hands and of all the limbs. The loss of pinprick perception in the hands was more extensive. In the feet there was analgesia on the right to the midfoot and on the left to the ankle.

On Oct. 23 the pyrexia became more severe without evident cause. On Oct. 27, as the anaemia and leucocytosis persisted (Hb 56%, W.B.C. 10,200—neutrophils 81%, eosinophils 2%), he was given a blood transfusion. During the following week he developed a cough and fever, with diarrhoea and signs of consolidation of the right lower lobe (Nov. 5). He was given a course of sulphapyridine, and the fever and diarrhoea cleared up. For a time he seemed to be losing ground, but at the end of November he was feeling better, the oedema was lessening, and no eosinophils were seen in a blood count (Hb 58%, W.B.C. 8,600—neutrophils 74%). The chest still gave many moist sounds. He continued to improve, though the hands and fingers were becoming contracted despite splinting and so on. At his own request he went home on Dec. 23, 1941, though he was still too weak to sit up in bed by himself.

Further Progress.—At home he remained in bed for three months, improving steadily. Six months after leaving the hospital he came to the out-patient department. His face was fat and ruddy; there was no oedema anywhere. Both hands were wasted and contracted—on the left a claw-hand, but on the right flexion at the metacarpophalangeal joints. The power in the upper arms and elbows was fair. The blood pressure was 245/150, and he had some morning headaches and giddiness. In Oct., 1942, he wrote to say that he was feeling fine; the left hand was still weak and contracted; but the right, which had been the worse, he was able to use for shaving and writing. The legs were still improving, and he could walk a mile or so.

Biopsy Reports.—A week after admission a biopsy specimen was taken of skin, subcutaneous tissue, and muscle from the back of the right forearm. The report on this was: "Slight chronic inflammation of fragment of skin, and fibrosis and degeneration of fragments of voluntary muscle. No evidence of polyarteritis nodosa." A second biopsy was made a month later (Oct. 9, 1941). The report on this was: "Degeneration and slight fibrosis of voluntary muscle. Changes consistent with polyarteritis nodosa in one small artery." (Fig. 5.)

FIG. 5.—Case III. Photomicrograph showing inflammatory reaction in vessel wall. Stained haematoxylin-eosin. ($\times 190$.)

Discussion

Three cases of polyarteritis nodosa, in which the diagnosis was confirmed by biopsy, were seen in 18 months. In a further case, clinically similar, the biopsies were negative. (This was a woman, aged 66, who had had diabetes mellitus and probably hypertension for years. She developed stiffness, pain, and weakness in both forearms, with paraesthesiae in the fingers. Much soft pitting oedema of the forearms occurred, with some contracture of the fingers. There was cardiac hypertrophy, but no evidence of congestive heart failure. She had high plasma proteins; total 7.6% (normal 5.6 to 7.8%)—albumin 5.35% (normal 3.4 to 4.9%), globulin 2.25% (normal 1.2 to 2.9%). After two months the right arm and hand improved; the left remained contracted. Though the clinical picture and the high plasma proteins closely resembled the three cases described below, two biopsies showed no evidence of polyarteritis nodosa; this case therefore cannot be considered as proved to be polyarteritis nodosa.)

The chief features of the three proved cases are summarized in the Table. They showed, as the salient features, localized soft oedema of the subcutaneous tissues of one or more limbs, with asymmetrical muscular weakness. The aetiology of polyarteritis nodosa is still without any definite conclusion, but it is interesting that two of the cases started with aches all over and the other shortly after a coryza. All three showed a leucocytosis, but eosinophilia was not a feature. Skin nodules were present in one case only. (Harris *et al.* (1939) pointed out that eosinophilia and nodules are too rare to be of practical value in diagnosis.) In the two cases in which the estimation was made, the total plasma proteins were very high owing to increase of plasma albumin. This finding may be of diagnostic value. The treatments employed were simple: rest in bed, a high vitamin diet supplemented by injections of vitamin B₁, and splinting and massage for the limbs. The progress of Case I suggests that it is possible to recover completely, while

in Case III there was apparently complete recovery from the acute attack, though certain sequelae remained.

Summary of Cases

	Case I	Case II	Case III
Sex and age	M. 27	M. 63	M. 58
Previous history	12 months' cough; recent coryza	Chronic bronchitis	2 years' recurrent bronchitis
Onset	Sudden weakness right arm and thigh	Pains in back and dyspnoea	Aches all over
Oedema	Right upper arm	Successively in ankles, left elbow, left thigh, right elbow, and both legs	Elbows, fore-arms, ankles, and lumbar region
Nodules	2 in skin of leg	None	In rectal mucosa
Muscular weakness ..	Right arm and thigh	Left wrist-drop, etc.	Right wrist-drop, etc.
Muscle tenderness ..	Yes	Yes	No
Contractures of hands ..	No	No	Yes (late)
Reflexes	—	Impaired or absent in affected limbs	Asymmetrically impaired
Sensory disturbance ..	None	Paraesthesiae	Paraesthesiae; anaesthesiae
B.P. on admission ..	135/85	150/110 (five weeks after admission)	200/110
Urinary abnormalities ..	None	None at first; then albumin, blood, and casts	Albumin ++
Lungs	Thickened pleura (x-ray)	Increasing bronchitis	Intercurrent pneumonia
Clubbing of nails .. .	Mild	Mild	None
Anaemia (Hb %) .. .	92%	77%, falling to 57%	68%, falling to 56%; normal six months later
Leucocytosis	12,000 and 12,000	6,200 to 22,000	10,200 to 7,200
Eosinophils %	0, 0	1, 0, 5, 4, 0, 0	4, 7, 2, 2, 0
Plasma proteins (%):			
Total (normal 5.6-7.8)	—	9.9	8.45
Albumin (" 3.4-4.9)	—	7.55	5.9
Globulin (" 1.2-2.9)	—	2.35	2.55
Biopsy	Positive	Positive	Neg. Pos.
Course of disease .. .	Recovered in one month. Remains well 2½ years later	Died after two months' illness	Recovered after six months; with residual contractures of hands and weakness of legs

Summary

Three cases showing localized soft oedema of the subcutaneous tissues of the limbs with asymmetrical muscular weakness are described. The diagnosis of polyarteritis nodosa was confirmed by biopsy. A large increase in plasma albumin was found in the two cases in which this estimation was done. One patient recovered completely, one recovered from the acute illness with muscular contractures and hypertension, and one died.

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The University Extension and Tutorial Classes Council, in co-operation with the Provisional National Council for Mental Health, will hold this year, provided enough applications are received, the usual course for medical practitioners on mental deficiency and allied conditions. The lectures will be given at the London School of Hygiene and Tropical Medicine, Keppel Street, Bloomsbury, and the date fixed for the course is April 24 to May 5. The University of London will grant certificates of attendance to those who attend regularly, taking both theoretical and practical work. The registration fee, to be paid at the time of application, is 10s. 6d., and the fee for the course is £5 15s. 6d. Cheques should be made payable to the Provisional National Council for Mental Health, and crossed Barclays Bank Ltd. All communications with reference to the course should be addressed to Miss Evelyn Fox, C.B.E., c/o University Extension Department, University of London, 39, Queen Anne Street, W.1. Intending candidates are asked to apply at the earliest possible date, but in any case by March 18. Detailed time-tables and other information will be sent out a week before the course opens to each person proposing to attend. Should the course have to be cancelled all fees will be returned.