Suid-Afrikaanse Tydskrif vir Geneeskunde
South African Medical Journal

Posbus 643, Kaapstad P.O. Box 643, Cape Town

Kaapstad, 11 Januarie 1958 Weekliks 2s. 6d. | Vol. 32 No. 2 | Cape Town, 11 January 1958 Weekly 2s. 6d.

'RHEUMATOID ARTHRITIS' ASSOCIATED WITH SPONTANEOUS GANGRENE OF THE EXTREMITIES

REPORT OF A CASE

S. BRINK, M.B., CH.B. (CAPE TOWN)

and

W. J. PEPLER, B.SC., M.D. (PRET.)

From the Department of Internal Medicine and the Institute for Pathology, University of Pretoria, Pretoria

Cases of spontaneous gangrene of the extremities have been described in association with many different conditions. They are not uncommon and the majority are clearly associated with some generalized disease process. The present report is based on observations of a patient with rheumatoid arthritis, myxoedema, and other pathological changes, who developed gangrene of the extremities while under observation in hospital. The differential diagnosis which was considered during life is discussed and the final diagnosis as verified at autopsy is presented.

CASE REPORT

M.E.M., a 57-year-old housewife, was admitted to hospital with a history that rheumatoid arthritic deformities of the limbs had developed over the past 4 years to such an extent that for 1 year before admission she was confined to bed. Since then she complained of progressive dysphagia, even with fluid substances, and frequent vomiting of profuse amounts of mucous material. She also complained of a husky voice, marked tiredness and a feeling of coldness.

The past history revealed two abortion episodes and there were no live children.

Examination

Rheumatoid arthritic deformities were present in the joints, with flexion deformities of the knee and elbow joints, ulnar deviation of the hands, and 'dropped feet'. She had a puffy face with periorbital oedema, a thickened tongue, a cold, dry and coarse skin, left facial nerve palsy and septic conjunctivitis. The blood pressure varied between 180/100 and 160/90 mm. Hg, and there was fairly marked arteriosclerosis. The liver was hard, non-tender and 3 fingers enlarged in the mid-clavicular line. The spleen was just palpable.

Laboratory Investigations

Blood count: Nothing abnormal.

Sedimentation rate: 55 mm. in the first hour (Westergren).

Urine examination: Albuminuria ++; no glycosuria or other abnormal findings.

Liver function tests: Total proteins 6·9 g. per 100 ml. Albumin 3·0 Globulin 3·9. Thymol flocculation ++++. Colloidal gold 5. Zinc sulphate 21.

Serum cholesterol 231 mg. per 100 ml.

Blood urea 63 mg. per 100 ml.

Protein-bound-iodine value: 2·1μg.%.

Radio-active iodine uptake of the thyroid: 6·6% after 5·6 hours and 3·9% after 24·7 hours.

ECG: Nothing of specific diagnostic value.

Barium swallow revealed a marked hold-up of barium about 3 inches above the diaphragm, with narrowing of the oesophagus from this point to just above the diaphragm, where a large diaphragmatic hernia could be demonstrated. Filling defects attributed to secondary oesophagitis were demonstrated above the constriction.

Treatment and Progress

The patient was given prednisone, 5 mg. t.d.s., and thyroid which was slowly increased to 1 gr. per day. At weekly intervals she received 40 units of ACTH intramuscularly.

After 3 months the myxoedema had completely disappeared. However, the patient became incontinent of urine and occasionally developed acute retention. At first this could be relieved by intermittent catheterization, but eventually an indwelling catheter was required.

After 7 months in hospital she developed an acute episode of dysphagia and profuse vomiting. Her general condition deteriorated suddenly but, with careful nursing and an almost completely liquid diet, she improved slightly. A week later peripheral gangrene developed, which involved firstly the tip of the left thumb and then the distal phalanx and the distal part of the middle phalanx of the right 4th finger in the course of a few days (Fig. 1). Finally

areas in two other fingers and the 4th left toe became gangrenous. The peripheral pulses remained easily palpable up to the edge of the gangrenous areas. A progressive generalized cold mauve mottling, the result of capillary dilatation, and an increased capillary fragility demonstrated by the blood-pressure-cuff test, were present.

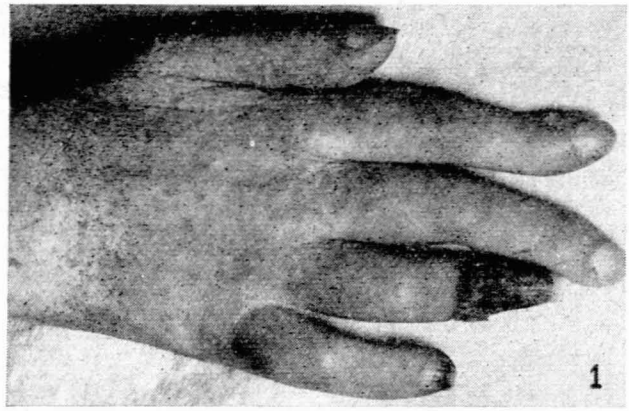

Fig. 1. Right hand with gangrene of the 4th finger and rheumatoid arthritic deformities of the joints.

At this stage no cryoglobulinaemia, porphyrinuria or haemoglobinuria could be demonstrated. The gangrene remained localized but the patient's general condition deteriorated steadily over a month and the dysphagia and vomiting increased. Terminal circulatory collapse occurred, and she died on 6 April 1957.

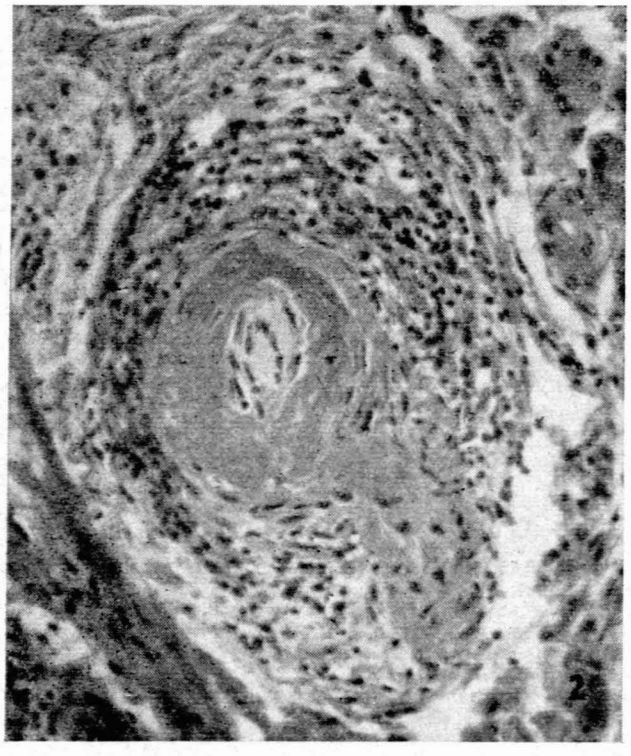

Fig. 2. Section through the wall of the pharynx showing an artery with typical features of acute periarteritis nodosa, H. & E.

Differential Diagnosis

The clinical problem in this case was to find a satisfactory explanation for the development of the spontaneous gangrene. Jepson[1] has recently provided a summary of most of the published work on cases of bilaterally symmetrical gangrene associated with unrelated conditions. These, as well as other conditions, were considered in this case.

Catchpole *et al.*[2] have stated that rheumatoid arthritis is frequently associated with diminution or redistribution of the peripheral blood flow. This may be due to organic arterial narrowing or occlusion, or alternatively to high resting tone in peripheral vessels although they may still be capable of relaxing to a normal calibre under certain conditions. Clinical recovery of rheumatoid arthritis under cortisone treatment was shown to be associated with increase in peripheral vasodilator response. This diminishes to below pre-cortisone levels if cortisone treatment is discontinued.

It was suggested that in this case the rheumatoid processes had progressed rapidly so that disturbances in vascular action had resulted in spite of the prednisone vasodilator attempt; that is to say, the vessels might have become unresponsive to the continued stimulus from prednisone. However, this did not explain the development of gangrene, which depends upon structural occlusion of the arteries, and cases of spontaneous gangrene of the extremities occurring in a patient with advanced rheumatoid arthritis under treatment with prednisone is very unusual.

Hypertension and arteriosclerosis were blamed as causative factors, but the blood pressure was only moderately high and arteriosclerotic changes during life were not very marked and were therefore excluded clinically as causes of the gangrene.

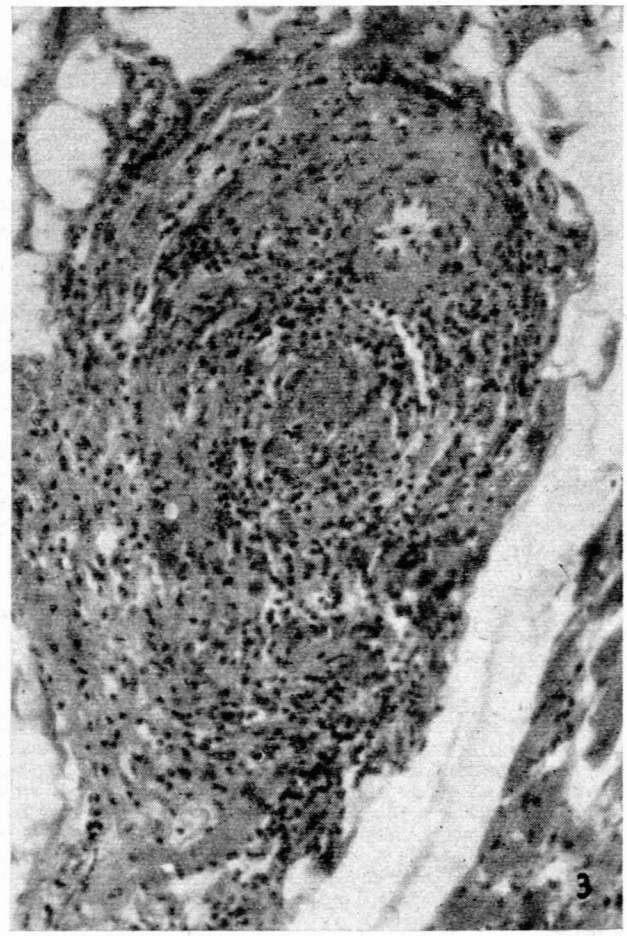

Fig. 3. Section of the calf muscle with lesions of acute periarteritis nodosa and atrophy of muscle fibres. H. & E.

Small embolic phenomena as causative factors were considered, but no source of emboli could be found.

Cryoglobulinaemia,[3] haemoglobinuria and porphyria, as well as diabetes mellitus and multiple myeloma with hyperglobulinaemia were excluded.

The *collagen diseases* were considered as a distinct possibility. The whole clinical picture with multiple system involvement, i.e. the rheumatoid type of arthritis, myxoedema, hypertension, hepatomegaly, splenomegaly, albuminuria, a left facial nerve palsy, and a large hiatus hernia with oesophageal stenosis, was suggestive of an atypical type of collagen disease. The post-mortem and microscopical examination confirmed this diagnosis.

Post-mortem Examination

Marked deformities of rheumatoid arthritis were evident. The muscles were markedly atrophic.

A bilateral obliterative pleuritis and pericarditis was present. The heart was enlarged, owing mainly to hypertrophy and dilatation of the left ventricle. There was a patchy fibrosis of the myocardium, but the endocardium and valves were normal. The coronary arteries were markedly sclerotic, but showed only slight linear fatty deposits in the intima. The aorta showed severe atheroma of both the thoracic and the abdominal portions, with ulceration, calcification, and ante-mortem thrombus formation.

The entire length of the oesophagus was diffusely thickened and signs of chronic oesophagitis were present. A 2-inch diameter hiatus hernia was demonstrated.

An acute haemorrhagic cystitis and an acute pyelonephritis localized to the left kidney was revealed.

The brain on section showed a small area of cerebral softening in the right cerebral hemisphere, which involved the upper part of the capsula intima and which had caused thickening of the ependyma of the floor of the lateral ventricle.

The thyroid was entirely replaced by dense fibrous tissue and macroscopically no thyroid tissue could be identified. However, this tissue was removed for microscopical examination.

Microscopical Examination. The tissues were fixed in 10% formalin for 1 week and blocks were taken and embedded in paraffin and cut at 4 microns. Sections were stained with haematoxylin and eosin, Verhoeff's stain for elastic tissue, Masson's trichromic stain, Mallory's phosphotungstic acid haematoxylin, and the periodic-acid Schiff stain.

Sections of the heart showed thickening of the pericardium and infiltration with lymphocytes. The myocardium showed hypertrophy of the muscle fibres, interstitial fibrosis, and a focal interstitial myocarditis. Slight fibro-elastic thickening of the left auricular endocardium was present. The coronary arteries showed well-marked concentric fibrous thickening of the intima, but no evidence of fat deposition.

The most significant morphological changes were observed in the arterioles throughout the body. These small vessels were the seat of severe obliterative endarteritis, and some showed the typical microscopic features of acute polyarteritis nodosa. Sections of the lungs, liver, pancreas, suprarenals and spleen revealed marked and widespread obliterative endarteritic changes. The hypertrophied muscular layers of the oesophagus and pharynx showed interstitial fibrosis with the endarteritic changes, and also typical lesions of acute polyarteritis nodosa (Fig. 2). At the periphery of the median nerve and the brachial artery, and in the vessels of the voluntary muscles of the calf, acute polyarteritis nodosa lesions were seen (Fig. 3). In addition, the calf muscles showed the features of disuse atrophy as well as foci of ischaemic necrosis.

The synovial membrane of the knee showed marked fibrous thickening, endarteritis obliterans, small foci of lymphocytic infiltration, areas of increased vascularization, and foci of deposition of altered blood pigment.

The vessels around the area of softening in the internal capsule were the seat of well-marked endarteritis, sometimes with total obliteration of the lumen. Well-marked atheroma of the basilar artery and severe endarteritic changes in some of the smaller vessels of the subarachnoid space were seen.

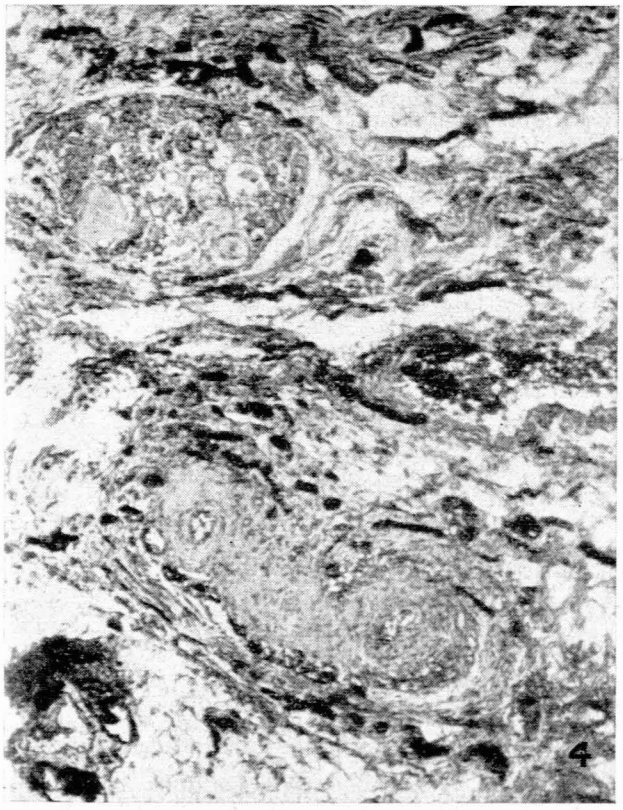

Fig. 4. Section of the pretracheal fibrous tissue in which remaining islets of thyroid tissue can be seen. The surrounding blood vessels are the seat of severe endarteritis. H. & E.

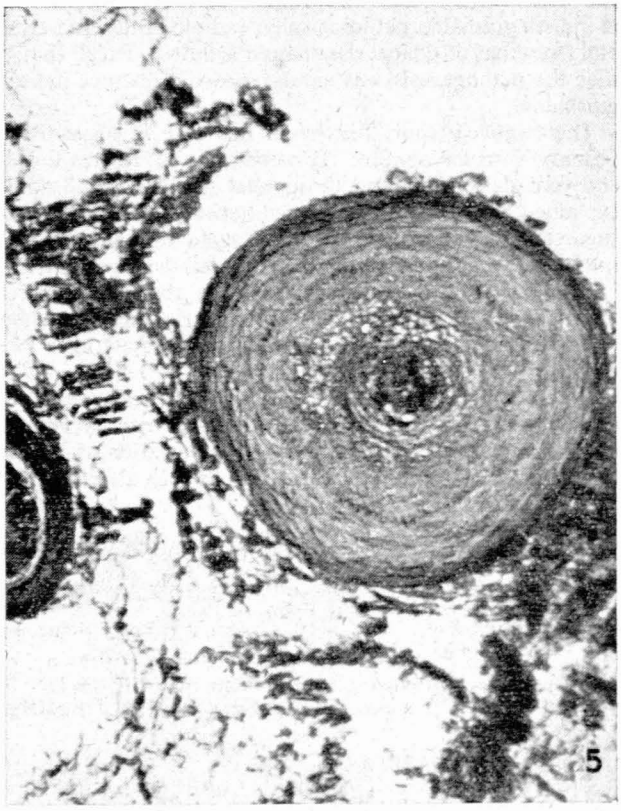

Fig. 5. Section of digital artery showing severe endarteritis and terminal occlusion by recently formed thrombus. H. & E.

Sections of the pretracheal fibrous tissue showed only an occasional islet of thyroid tissue composed of 5-6 acini. The islets were surrounded by dense hyaline fibrous tissue. The blood vessels in the fibrous tissue showed signs of (*a*) acute polyarteritis nodosa and (*b*) pronounced obliterative endarteritis (Fig. 4).

A section taken through the index finger of the right hand showed marked obliterative endarteritis of the digital arteries. In addition the one artery was completely occluded by a small recently formed thrombus (Fig. 5).

The kidneys showed the histological features of acute pyelonephritis and well-marked hyalinization of the afferent arterioles.

Staining of the pituitary with the P.A.S. Orange G method revealed normal thyrotrophic cells.

DISCUSSION

Pathologically this case presented further problems in that it was difficult to assess the exact relationship between the various possible disease processes, viz. polyarteritis nodosa, obliterative endarteritis, myxoedema, and rheumatoid arthritis.

The various syndromes comprising the collagen diseases are usually well defined clinically and pathologically, though cases showing more than one syndrome are frequently encountered. Thus Ball[4] suggested that although polyarteritis nodosa is a rare complication of rheumatoid arthritis, the association of these two conditions is more than coincidental. The frequency, distribution and morphology of arterial lesions in rheumatoid arthritis are variable, ranging from mild indeterminate arteritis to classical polyarteritis nodosa. Rose[5] has found the incidence of rheumatoid arthritis in polyarteritis nodosa to be about 8% as opposed to 1% in the general population. On the other hand, Friedman *et al.*[6] has demonstrated that the arthritis of polyarteritis nodosa is indistinguishable pathologically, radiologically and clinically from that of typical rheumatoid arthritis. Pagel[7] thought that the pathogenesis was similar and the features indistinguishable.

The relatively short history in this case is suggestive of primary vascular disease. However, the widespread obliterative endarteritis found throughout the body could not be explained on the basis of polyarteritis nodosa and it is suggested that it may have been due to prolonged arterial spasm with final thrombotic occlusion of the digital arteries.

The very severe vascular lesions in the region of the thyroid—polyarteritic changes as well as obliterative endarteritis—suggests that thyroid atrophy may have been secondary to vascular disease.

Recently Fisher[8] described a case of classical rheumatoid arthritis of 15 years' duration with lesions of polyarteritis nodosa revealed at post-mortem. The association of rheumatoid arthritis and rheumatic heart disease has also frequently been stressed. Such an association emphasizes once more the similarities between rheumatoid arthritis and other diseases that are characterized by disseminated vascular lesions, necrosis of collagen, pathological changes in the joints, and cardiac lesions that *may* have a common pathogenic factor, particularly hypersensitivity.

It has also been suggested that the occurrence of disseminated vascular lesions and other visceral manifestations in patients with rheumatoid arthritis may be the result of therapy with steroids. In most such cases, however, these lesions seem to be more representative of rheumatoid arthritis than of polyarteritis nodosa. There is, however, a suggestion that treatment with steroids will lead to a higher incidence of visceral and vascular manifestations in rheumatoid arthritis (Kemper *et al.*[9]).

SUMMARY

1. A case of spontaneous gangrene of the extremities in a patient with rheumatoid arthritic deformities and myxoedema is presented.

2. The differential diagnosis of cases of spontaneous gangrene of the extremities with palpable peripheral pulses is discussed.

3. Autopsy revealed the presence of polyarteritis nodosa and it is suggested that this was probably the primary lesion leading to the development of arthritic deformities and myxoedema.

4. In addition widespread endarteritic changes were present which could only be explained on the basis of prolonged vascular spasm.

We should like to express our thanks to Prof. H. W. Snyman and Dr. L. D. Erasmus for encouragement and advice, Prof. J. Barnetson for reading the manuscript, and the Superintendent of the Pretoria General Hospital for permission to publish the case.

This work was supported by a grant from the Council for Scientific and Industrial Research.

REFERENCES

1. Jepson, R. P. (1956): Circulation, **14,** 1084.
2. Catchpole, B. N., Jepson, R. P. and Kellgren, J. H. (1954): Ann. Rheum. Dis., **13,** 302.
3. Stats, D., Jesse, G. M. and Bullowa, J. G. M. (1943): Arch. Intern. Med., **72,** 506.
4. Ball, J. (1954): Ann. Rheum. Dis., **13,** 277.
5. Rose, G. (1953): Cited by Ball.[4]
6. Friedman, H. H., Swartz, S., Trubek, M. and Steinbrocker, O. (1953): Ann. Intern. Med., **38,** 732.
7. Pagel, W. (1951): J. Clin. Path., **4,** 137 and 157.
8. Fischer, E. R. (1957): Amer. J. Clin. Path., **27,** 191.
9. Kemper, J. W., Baggentoss, A. H. and Slocumb, C. H. (1957): Ann. Intern. Med., **46,** 831.