TIGHTNESS OF THE SKIN OVER THE FEET AND LOWER LIMBS ASSOCIATED WITH HAEMOSIDEROSIS

JOHN I. FORBES, M.B., M.R.C.P. (EDIN.), D.T.M. & H., *Harare Hospital, Salisbury, Rhodesia*

Iron overload is known to be common in the Bantu of Southern Africa, and an incidence of 40 - 88% has been recorded in various investigations.[1] The siderosis is most marked in the liver and reticulo-endothelial system and it reaches its greatest degree between the ages of 40 and 50 years.[2] It has been suggested, though not universally accepted, that the presence of iron in the portal tracts of the liver might provoke cirrhosis, especially in the presence of chronic malnutrition.[3] In advanced cases of Bantu siderosis there may also be widespread deposition of iron in epithelial tissues. Indeed, the histological picture may be indistinguishable from that of idiopathic haemochromatosis which McDonald[4] believes to be a variant of alcoholic cirrhosis occurring in subjects exposed to high iron diets, rather than a specific metabolic disorder in which excessive amounts of iron are absorbed from a normal diet.

In Rhodesia siderosis is probably much more common than is generally realized. In a series of 134 unselected autopsies carried out on adults over the age of 20 years at Harare Central Hospital, Buchanan[5] found 84 with stainable iron in the liver—an incidence of 62·7%, while if only the males are considered, the incidence rises to 76·3%. Moreover, of the 93 males in this series, no fewer than 48 (51%) were found to have moderate or heavy deposits of iron in the liver. On the other hand, deposition of iron in the skin is much less common, and in only 2 of Buchanan's cases was this feature found; both of these were males who had postnecrotic cirrhosis of the liver and pancreatic fibrosis with heavy deposits of iron in the liver, pancreas and heart. Thus it seems likely that iron deposition in the skin only occurs in the more advanced cases of iron overload in the African.

Despite the large amount of work which has been done on Bantu siderosis, no characteristic skin change appears to have been described. The classical appearance of skin resulting from iron deposition is, of course, pigmentation which may consist of a bronzing due to increased melanin or a slate-grey discolouration due to the presence of iron itself. Atrophy of the epidermis may accompany the pigmentation and give the skin a fine, soft texture, but contraction and tightening of the skin does not appear to have been described as a feature. It would seem of some interest, therefore, to report 3 cases in which this association has been found.

CASE REPORTS

Case 1

Jackson, an African male patient aged about 55 years, was admitted to Harare Hospital on 13 February 1963 complaining of backache and pain in the left leg. The most striking feature on clinical examination was that the skin over both legs appeared tightly contracted and was adherent to the subcutaneous tissues. It was also noted that his skin was generally darker than normal and that his tongue was pigmented, though he said he had been born with a dark skin and that the other members of his family were similar in appearance. His hair was rather fine and scanty, and a firm liver was palpable 2 fingerbreadths below the right costal region.

Investigations showed anaemia (Hb. 63%), a leucopenia (WBC 2,800/cu.mm. with 51% neutrophils and 49% lymphocytes) and a raised ESR (64 mm. in 1 hr.). Urine and stool examinations were normal, but liver-function tests were deranged (alkaline phosphatase 30 KA units, zinc sulphate turbidity 12 units and thymol flocculation positive), and there was a marked inversion of the A/G ratio—albumin 1·6 G/100 ml. and globulin 5·8 G/100 ml., but direct serum Van den Bergh was negative and serum bilirubin was normal at 0·4 mg./100 ml. Urinary porphyrins were absent, blood urea was 39 mg./100 ml. and serum electrolytes, serum calcium and serum inorganic phosphorus were within normal limits.

It was thought that this patient was suffering from a collagen disease such as dermatomyositis or scleroderma, and a skin and muscle biopsy was performed. Dr. Buchanan reported: 'Section of the skin shows a scanty, patchy chronic inflammatory cell exudate in the dermis. The dermal collagen exhibits degenerative changes. Deposits of haemosiderin pigment are also seen.

'Sections of muscle show extensive replacement of the muscle fibres with fibrous tissue among which are seen focal collections of lymphocytes. There are also extensive deposits of haemosiderin pigment. This looks most like an area of old trauma, but could possibly be advanced dermatomyositis. The

haemosiderin pigment, however, would be difficult to explain if the second diagnosis was correct.'

Before further investigations could be carried out the patient suddenly became pyrexial. His condition deteriorated rapidly and he died within 48 hours. An autopsy was performed (Dr. Buchanan) and death was found to be due to 'acute generalized peritonitis in a case of haemochromatosis'. Heavy deposits of siderin were found in the skin, skeletal muscle, heart muscle, lymph nodes, spleen, pancreas and kidney, and the liver showed a fine cirrhosis with heavy deposits of haemosiderin especially in the fibrous bands.

Case 2

Muhlabati, aged about 60 years, was admitted on 25 February 1965 complaining of a constant burning pain in both feet of several weeks' duration. The pain varied in intensity and was temporarily relieved by immersing his feet in warm water. He volunteered no other complaints, but admitted on questioning to a non-productive cough. His diet seemed reasonably adequate with meat 3 times a week and occasional milk in addition to the basic maize meal and vegetables. He said he had never been a heavy drinker, but for many years had enjoyed about 1 pint of African beer daily. He stopped drinking altogether in 1945 on the advice of a doctor who took his appendix out, but he did not know the reason for this advice.

The most significant finding on physical examination was that the skin over both feet and the lower thirds of both legs was firmly adherent to the underlying tissues and tightly stretched (Fig. 1). The feet were warm, the peripheral pulses were easily palpable, and there were no signs of venous stasis.

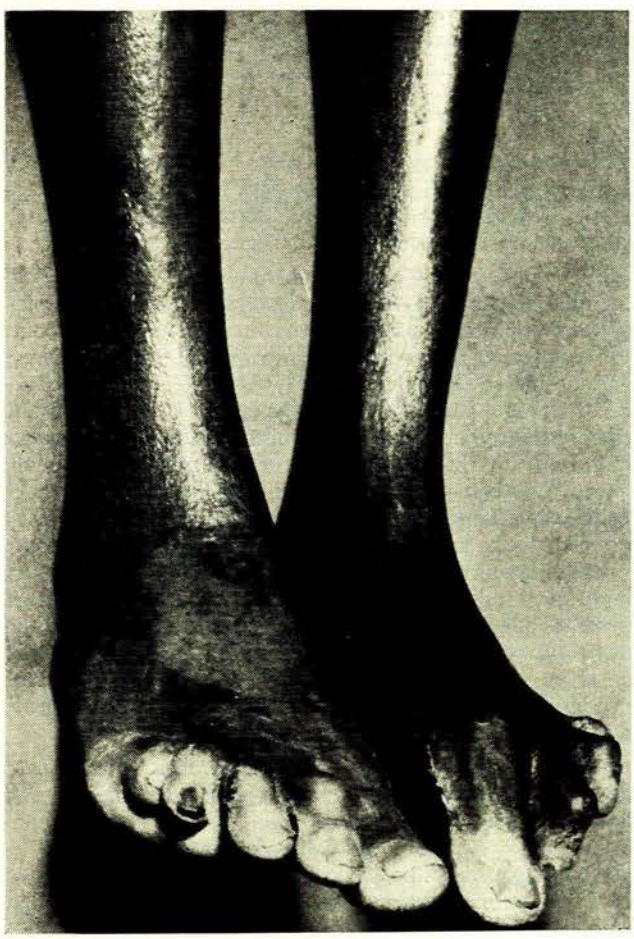

Fig. 1. The appearance of the skin over the feet in case 2.

The remainder of the patient's skin was normal and easily pinched up, but the palms of both hands were slate-grey in colour. The hair on his head was plentiful, but very fine in texture and rather straight. Clinical examination revealed no other abnormality except for a few rhonchi in the right chest. Neurological examination of the feet was normal.

The skin changes in this case were almost identical with those of the previous case, so a clinical diagnosis of siderosis was made and was confirmed by a skin biopsy from the right ankle, which showed heavy deposits of iron in histiocytes and particularly around the appendages, and by a liver biopsy which showed minimal portal fibrosis with very dense haemosiderin deposits in the portal tracts and moderate deposits in the liver cells.

Other investigations were as follows: Hb. 80% (12·0 G/100 ml.); WBC 4,000/cu.mm.; neutrophils 53%, lymphocytes 46%, eosinophils 1%. ESR 100 mm. in 1 hr. (Westergren). Urine normal. The glucose-tolerance test showed a diabetic type of curve with a normal fasting level at 80 mg./100 ml. and a delayed peak at 2 hrs. of 170 mg./100 ml.

Liver-function tests: direct Van den Bergh negative. Serum bilirubin 0·2 mg./100 ml. Alkaline phosphatase 4·5 KA units, zinc sulphate turbidity 16 units, thymol flocculation positive. Serum protein 6·8 G/100 ml., serum albumin 2·7 G/100 ml., serum globulin 4·1 G/100 ml., A/G ratio 0·7:1. Prothrombin time 19 seconds, prothrombin index 74%.

The serum iron levels were 20 μg./100 ml. on 4 March 1965, 88 μg./100 ml. on 15 March 1965 and 135 μg./100 ml. on 23 April 1965. Total iron-binding capacity was 300 μg./100 ml. (23 April 1965). Stool examination showed no ova to be present. Total fatty acids 3·6 G/24 hours. Serum lipase: 7·7 units %.

X-ray of the chest showed a mottled opacity in the right upper lobe suggestive of an old tuberculous lesion. Repeated examination of sputum showed absence of acid-fast bacilli.

It was decided to try the effect of desferrioxamine B mesylate as a chelating agent in this case, and the patient was given Desferal, 400 mg. intramuscularly, thrice daily for 3 days. The increase in urinary iron excretion is shown in Fig. 2, and long-term therapy was suggested, but the patient refused to remain in hospital and, as he lived on a farm, outpatient treatment was not feasible. On discharge he said the pain in his feet was considerably less severe though still present.

Case 3

Enock, aged 56 years, was admitted on 18 May 1965 complaining of pain and stiffness of both ankles of 5 months' duration. He had been in another hospital for 3 months on treatment for bilateral tuberculosis of the ankles, and was referred to Harare Hospital because he was not responding. He had no other complaints, and specific questioning revealed no relevant information. He denied any previous illnesses. His diet seemed adequate with meat daily, occasional fish and frequent sour milk in addition to the basic maize meal. He said he had taken no alcohol whatever (for religious reasons) until 2 years ago. Since then, his alcohol intake had consisted of 2 mugs of African beer weekly.

On physical examination the skin over both feet and lower legs was contracted and tightly adherent to underlying tissues with an identical appearance and feel to that of the previous 2 cases. There were no signs of venous stasis and peripheral pulses were easily palpable. Movement of the ankle-joints was free and painless. The skin over the rest of the body was normal, but the palms of the hands were again rather slate-coloured. Systemic examination was normal except for the finding of a firm splenomegaly, 2 fingerbreadths below the left costal margin. The liver was not palpable.

Skin biopsies were taken from the postero-medial aspect of the left lower leg and from the left forearm and Dr. Ross reported: 'Perl's stain shows extensive haemosiderin deposits in the biopsy from the leg, but none in that from the arm. The iron pigment is mainly present in the deeper dermis and tends to be accumulated around vessels, hair follicles and sweat glands.'

A liver biopsy was attempted twice, but no specimen was obtained, and further attempts did not seem justified. Other investigations were as follows: Hb. 86% (12·8 G/100 ml.); WBC 4,000/cu.mm.; neutrophils 57%, lymphocytes 38%, monocytes

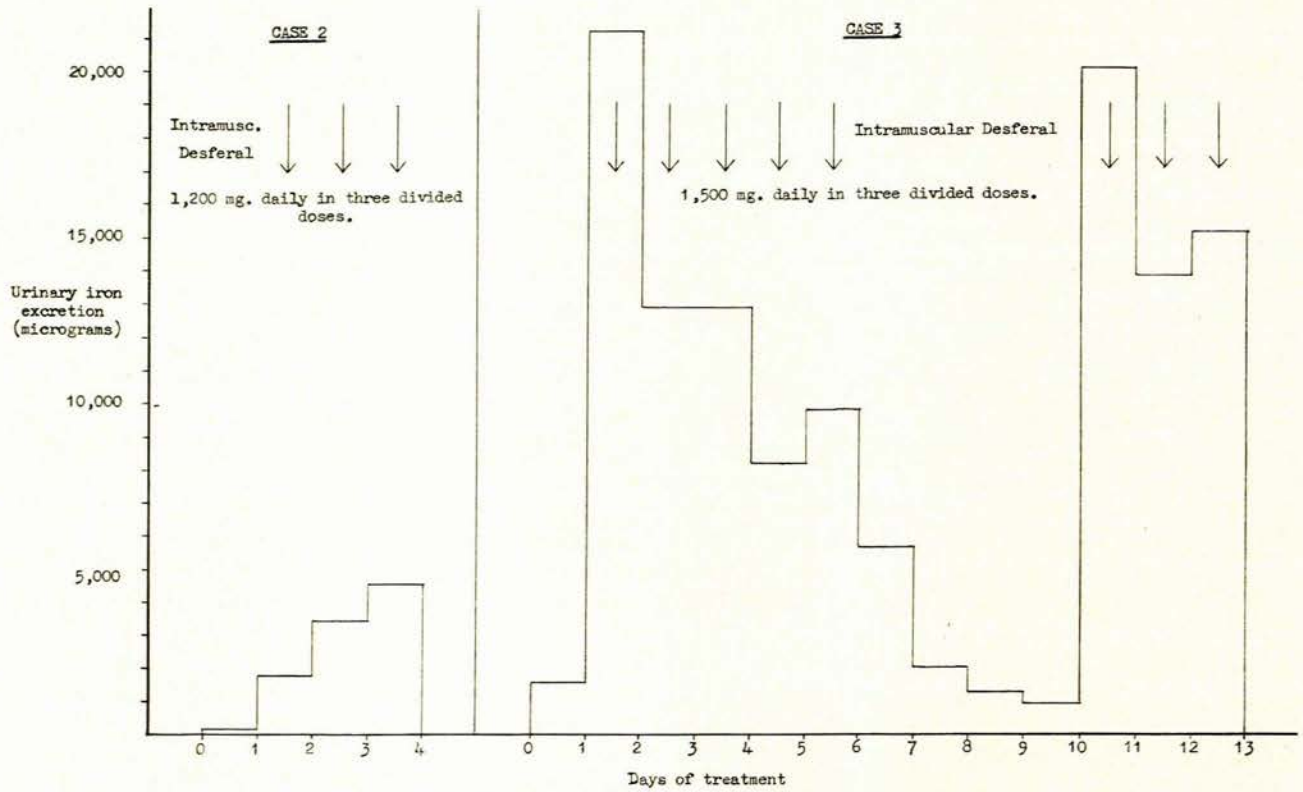

Fig. 2. The response to desferrioxamine B mesylate in cases 2 and 3.

1%, eosinophils 4%. ESR 8mm. in 1 hr. (Westergren). Urine analysis showed albumin + leucocytes + hyaline casts. No glycosuria. Urinary porphyrins absent on 3 occasions.

Liver-function tests: direct Van den Bergh negative. Serum bilirubin 1·6 mg./100 ml. Alkaline phosphatase 4·0 KA units, thymol turbidity 4·0 units, thymol flocculation positive. Serum protein 9·0 G/100 ml., serum albumin 2·4 G/100 ml., serum globulin 6·6 G/100 ml., A/G ratio 0·36:1. Plasma protein electrophoresis showed a raised gammaglobulin fraction. Prothrombin time 20 seconds, prothrombin index 85%.

The glucose-tolerance test showed a diabetic curve with fasting level of 150 mg./100 ml. and subsequent levels at ½-hour intervals of 180, 205, 170, 120, and 170 mg./100 ml. D-xylose excretion 1·5 G in 5 hours (normal > 4 G in 5 hours). Serum lipase 2·5 units/100 ml., serum amylase 258 Somogyi units. Stool fatty acid content 5·7 G/24 hours. Unsplit fats 1·9 G/24 hours. Percentage 'split' fats 67%.

X-ray of the chest showed no abnormality. Barium follow-through showed a normal small bowel pattern. Serum iron 250 μg./100 ml. (18 June 1965), 220 μg./100 ml. (28 June 1965) and 225 μg./100 ml. (5 July 1965). Iron-binding capacity 295 μg./100 ml. (18 June), 320 μg./100 ml. (28 June) and 275 μg./100 ml. (5 July 1965).

The response to the first 2 weeks of therapy with desferrioxamine B mesylate, 500 mg. intramuscularly thrice daily, is shown in Fig. 2. Intermittent therapy was given because this has been found to be more effective than continuous therapy. No objective change in the appearance of the patient's skin was observed but his pain decreased steadily and within 3 weeks he said his feet and legs were completely free from any discomfort. Therapy was continued for a total period of 31 days, after which the patient insisted he was perfectly well and must go home.

DISCUSSION

Tightness of the skin is a typical feature of scleroderma, in which it is usually preceded by oedema of the affected part, often with Raynaud's phenomenon. Furthermore, progressive scleroderma may initially involve the feet only, though it usually spreads to affect other parts of the body, particularly the face, neck and upper trunk.

Skin tightness and contraction have also been observed to follow oedema of the feet and legs of varied aetiology. Gelfand[6] reported it as a sequel to the oedema of both cardiac failure and the nephrotic syndrome in African subjects and considered that it might take only 2 - 3 weeks to develop. The main histological change in his cases was in the nature of chronic inflammation, and there was no evidence of atrophy of the epidermis or of scleroderma. It would appear, however, that the sections in his cases were not specifically stained for iron, so it seems possible that they too may have been cases of haemosiderosis and that the oedema may have been incidental or of minor contributory importance to the development of their skin tightness. Oedema due to conditions such as cardiac failure and nephrotic syndrome is extremely common in patients of all races, and there must surely be some other factor responsible for the very few cases, all apparently African, in whom skin contraction develops.

Loewenthal[7] described 11 cases of chronic oedema leading to a verrucose condition of the skin over the feet and he suggested the name lymphostatic verrucosis for this condition, which Gelfand[6] has compared with that shown by his cases. However, the clinical and histological features of the 2 groups seem quite distinct, and I do not believe that lymphostatic verrucosis has any relationship to the cases of skin tightness described by Gelfand or with the 3 cases

reported here, all of which seem to have shown strikingly similar skin changes.

The suggestion that in these 3 cases the skin tightness over the lower legs and feet was associated with iron deposition might be criticized on the grounds that deposits of haemosiderin frequently occur in the legs in association with stasis dermatitis and other vascular disturbances,[8] or that the lower legs are particularly exposed to trauma which could lead to iron accumulation. No evidence of venous stasis was found in these cases, and in the first 2 extensive iron deposition was found in internal organs as well as in the skin over the lower legs. In the third case a liver biopsy was unfortunately unsuccessful, and no iron was found in a biopsy of skin taken from the patient's arm. However, the biopsy specimen from the leg of this case was deliberately taken from the postero-medial aspect of the lower calf where trauma should be minimal but where the skin tightness was obvious. Furthermore, in this case, the high serum iron and percentage saturation and the diabetic type glucose-tolerance curve were consistent with a diagnosis of excessive iron storage.

An unusual feature of the second case was that the serum iron level was not elevated on any of 3 occasions it was estimated, whereas a saturated transferrin appears to be a prerequisite for parenchymal iron loading. A possible explanation is that the factors responsible for the excess iron load in this patient were no longer operative by the time he came into hospital. The serum iron level is lowered in conditions such as carcinoma and chronic infection, but it seems unlikely that the chronic pulmonary infection (presumed inactive tuberculosis) could have played any significant part in this respect. In view of the low serum iron levels and the low percentage saturation of iron-binding capacity (45%) there seemed to be some doubt as to whether iron chelating agents would be effective in increasing iron excretion, since it has been pointed out by Sephton-Smith[9] that desferrioxamine causes efficient excretion of iron only when the iron-binding capacity of the plasma is almost totally saturated and iron stores are increased. The response in this case was not marked by comparison with that obtained in other cases of iron overload and it was unusual in that iron excretion progressively increased from day to day up to 4,560 μg. on the third day of treatment, whereas the maximal response usually occurs on the first day. In case 3, where the iron-binding capacity of the plasma was more fully saturated, the response to Desferal was greater and it followed the usual pattern of a maximal initial response (21,200 μg. on the first day of treatment) with subsequent decline.

It is unfortunate that neither of these patients would consent to long-term therapy as it would have been most interesting to observe whether any reversal of the skin changes could be produced. Wöhler[10] has shown that patients with haemochromatosis often lose their bronze colour after only 2 - 3 weeks of treatment with desferrioxamine, and histologically this is due to reduction in the melanin content of the basal cell layer rather than any definite decrease in iron. Wöhler also remarked on the rapid subjective improvement of his patients and suggested that this was due to beneficial effects on oxidative metabolic processes rather than the incipient excretion of iron. Therapy was not continued long enough in case 2 for any relief of symptoms or signs to be observed, but subjective improvement in case 3 was striking though no significant objective change was noted.

The aetiology of the haemosiderosis in these patients remains obscure. There was no history of multiple blood transfusions nor evidence of any chronic haemolytic process, though case 1 was moderately anaemic. The association between excessive consumption of alcohol and the development of iron overload is well known and is probably due both to the excessive amount of iron present in the fermented beverages consumed,[11] and to the increased absorption of iron brought about by alcohol.[12] Unfortunately, details of alcohol consumption were not obtained from the first patient but both the others denied having consumed excessive quantities at any time of their lives—though the fact that the second patient was advised to stop drinking in 1945 suggests that he might previously have been imbibing more than he admitted.

A deficiency of the exocrine secretions of the pancreas has been shown to be associated with excessive iron absorption. No evidence of such deficiency was obtained in the first 2 cases, while in the third, although there was some evidence suggestive of malabsorption, this did not seem, from stool fat analysis and serum lipase estimation, to be related to pancreatic deficiency. Duodenal intubation to obtain a specimen of duodenal juice was refused by this patient.

Excessive iron absorption has been found to occur in some cirrhotic patients even when the body stores are normal or increased.[13] Cirrhosis was found in 2 of the cases reported by Conrad *et al.*,[13] but in the first case it was described as a 'fine cirrhosis' and in the second as a 'minimal portal fibrosis', so it does not seem to have been a very marked feature of their disease. Several experimental studies have shown increased iron absorption when the diet is high in iron, but low in certain nutrients, including protein and phosphate, and it seems worthy of note that the first 2 patients reported had fine, straight hair—a feature commonly seen in protein malnutrition—and all three had low serum albumin levels with reversed A/G ratios.

SUMMARY

Three cases presenting with painful lower limbs are reported. In each case the striking clinical feature was tightness of the skin over the feet and lower legs, and each of the patients was found to have haemosiderosis. It is suggested that there is a relationship between these 2 conditions, and that patients presenting with pain and skin tightness should be investigated for iron overload.

Therapy with an iron chelating agent gave striking subjective relief in one case and it seems possible that long-term therapy might produce objective improvement in the skin condition. Some of the aetiological factors concerned in haemosiderosis are briefly discussed.

The Desferal used in these cases was kindly supplied by Dr. T. D. Bleakley, of the CIBA Clinical Research Department, to whom I am most grateful. I also wish to thank Dr. M. Webster, Secretary for Health for Rhodesia, for permission to publish this paper.

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