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Julius Smith
Luiz Felipe B. Mello
Norberto C. Nogueira Neto
Walter Meohas
Luciana W. Pinto
Viviane A. Campos
Maysa G. Barcellos
Nelson Jabour Fiod
José Francisco Neto Rezende
Carlos Eduardo L. Cabral

Malignancy in chronic ulcers and scars of the leg (Marjolin's ulcer): a study of 21 patients

J. Smith, M.D., M.R.C.P., F.R.C.R.
L.F.B. Mello, M.D.
N.C. Nogueira Neto, M.D.
V. A. Campos, M.D. · M.G. Barcellos, M.D.
C.E.L. Cabral, M.D.
Department of Radiology,
National Cancer Institute – INCA,
Rio de Janeiro-RJ, Brazil

J. Smith, M.D., M.R.C.P., F.R.C.R. (✉)
Rua Humberto de Campos,
974/1301 (Leblon)
22430–190 Rio de Janeiro-RJ, Brazil

W. Meohas, M.D. · N.J. Fiod, M.D.
J.F.N. Rezende, M.D.
Department of Surgery
(Bone and Soft Tissue Service – TOC),
National Cancer Institute – INCA,
Rio de Janeiro-RJ, Brazil

L.W. Pinto, M.D.
Department of Surgical Pathology,
National Cancer Institute – INCA,
Rio de Janeiro-RJ, Brazil

Abstract *Objective*. To study the imaging features of patients with chronic ulcers of the leg that were associated with malignancy.
Design and patients. All patients who on biopsy were proven to have malignancy – the majority of which were squamous cell carcinoma – were included in a prospective study. Ulcers limited to the foot were excluded but ulcers of the leg which extended into the foot were included. Amputation was performed in all but two patients, due to pain, bleeding or tissue necrosis.
Results. The etiology was multifactorial. The mean duration of the ulcers was 36 years including venous ulcers, extensive scarring of the leg secondary to infection, injury or burns. One ulcer was secondary to a snake bite. The remainder, usually in the upper part of the leg, had repeated episodes of blunt trauma or knife wounds, which were also complicated by infections which failed to heal or, if they healed, regularly recurred. Although arterial insufficiency was not primary in any patient, most were of advanced age and it may have been an element in some patients. Despite infection, osteomyelitis was present in only one patient. The essential features were bone destruction, soft tissue mass and periosteal reaction. The bone destruction was visible on the radiographs in all but one case. The soft tissue masses varied in size but in general were very large. The periosteal reaction varied in type but most commonly was lamellated. The classic undulating solid periosteal reaction of venous stasis was only occasionally present. The periosteal reaction was nonspecific in the majority of cases and did not aid in the diagnosis or etiology. MRI and CT studies were performed in six patients. These were helpful in defining the extent of bone destruction and periosteal reaction but were not essential in management.
Conclusion. Chronic ulcer present for decades that then undergoes malignant change is a disease of developing countries where patients only consult physicians when they have developed complications such as pain, bleeding or tissue necrosis. Chronic ulcers may require to be biopsied at regular intervals as malignant change in these ulcers is directly related to their duration.

Keywords Chronic ulcers · Leg ulcers · Squamous cell carcinoma · Sarcoma · Amputation

Introduction

Chronic ulcers of the leg are common throughout the world and are responsible for considerable morbidity. It is estimated that in the United States and the United Kingdom the incidence approaches 1% [1, 2, 3]. In developing countries they are much more common, although no accurate statistics are available. While malignancy developing in these ulcers in the developed world [4, 5] is distinctly uncommon, this complication is not rare in developing countries.

A prospective study was undertaken of patients with malignancy developing in chronic ulcers of the leg over a 2-year period from August 1996 to July 1998, to evaluate the actual numbers of these patients, to study the radiological features and to correlate them with the pathological findings. The etiology was evaluated where possible.

Materials and methods

Patients with chronic ulcers that on biopsy showed malignant change were entered into the study. Most commonly these were squamous cell carcinomas but there were three sarcomas, which were classified as fibrosarcoma, malignant fibrous histiocytoma and osteosarcoma. These patients were referred to our soft tissue and bone tumor clinic (TOC) and were entered into our prospective study as they presented.

Bone destruction is the most important radiological finding for the surgeon. It was found in every patient who underwent amputation. In only one patient was it not seen on the radiographs, and this was due to the suboptimal quality of the radiographs.

The most valuable study in these patients was MRI. It demonstrated the margins of destruction and extent very well. It also was better than CT at demonstrating the soft tissue mass. Unfortunately the periosteal reaction is poorly imaged on MRI. However, the periosteal reaction was not important for the diagnosis of malignancy. It was present in some degree in all patients but the type and extent bore no relationship to the size and etiology of the ulcer. It is clear that MRI is the superior technique.

Patients in whom the ulcers were limited to the foot were excluded but leg ulcers that extended partly into the foot were included. All patients had complete clinical histories and detailed clinical examinations. A social history was also obtained by a professional social worker in our earlier cases, in an attempt to explain the chronicity of these ulcers. This was difficult and also noncontributory as the trial proceeded, and was terminated.

All patients had routine radiographs of the leg and also routine frontal and sagittal radiographs of the chest. CT or MRI examinations were not undertaken in all patients as this was frequently impossible due to the great demands placed on limited equipment in a busy cancer hospital. Frequently cross-sectional imaging studies were not arranged prior to amputations, and when patients were admitted to the hospital for surgical resection operations could not be delayed. T1- and T2-weighted sequences could not be performed in multiple planes on all patients due to limited access to MRI equipment, and T1-weighted studies alone were performed in many patients. Contrast injection was used in only two patients.

Routine hematological tests, including the erythrocyte sedimentation rate, were performed on all patients. Biochemical tests on a sequential multiplanar analyzer were not performed routinely. Individual tests such as serum calcium and phosphate, and alka-

Table 1 WHO grading of squamous cell carcinoma, based on the proportion of mature cells present in the tumor

Grade I	More than 75% of the cells are differentiated
Grade II	– More than 50% of the cells are differentiated
Grade iii	– Less than 25% of the cells are differentiated

line phosphatase, were performed on most patients. Blood urea and liver function tests were performed as indicated.

Particular attention was paid to inguinal node enlargement, and this was noted in all patients.

All tumors were graded on a scale of I to III based on the World Health Organization criteria (Table 1). The surgical amputation specimens were correlated with the radiological findings.

Radiologically three parameters in particular were studied, namely soft tissue mass, bone destruction and the periosteal reaction. The extent of bone destruction and the size of the mass were categorized as: minor, 0–5 cm; moderate, 5–10 cm; large, 10–15 cm; very large, 15–20 cm; massive, over 20 cm. The periosteal reaction was described as regards type and extent.

Results

The age range of the patients was 48–81 years with a mean of 76 years, and the M:F ratio was 11:10. The mean latent period from the date of origin of the ulcer to the development of carcinoma or sarcoma was 36 years.

Enlarged inguinal lymph nodes were found in six (30%) patients. These patients underwent needle aspiration biopsy and one patient only was found to have malignant cells. The lymph nodes in this patient were excised prior to amputation.

Nine of the patients had chronic ulcers in the area between calf and foot, mostly related to the medial malleolus, but many had ulcers which involved the whole circumference of the leg. These had pigment changes commonly found in the skin and also thickening. These were clinically venous ulcers.

The remainder of the patients had extensive scarring of the leg related to frequently repeated trauma either with knives or blunt wounding. Previous extensive burns had occurred in three patients and one had been bitten by a venomous snake [6] which resulted in infection and secondary scarring.

The cases with squamous cell carcinoma (SCC) could be divided etiologically into those with venous ulcer (n=9) and those with burns (n=3). The other patients had a nonspecific etiology for their ulcers that was multifactorial, related to extensive scarring which followed trauma from either sharp or blunt instruments. There was frequently infection. In only one patient could no etiological factor be identified.

Of the sarcomas that developed in some patients, two were related to long-standing venous ulcers and the third was secondary to chronic osteomyelitis which had followed a long-standing ulcer that had resulted in osteosarcoma.

Table 2 Summary of the radiological findings

Case no.	Age (years)/ Sex	Duration (years)	Size (cm)	Grade	Bone destruction	Soft Tissue Mass	Periosteal reaction
1	80/F	40	20×17	I	Minor	Minor	Minimal; lamellated interrupted
2	62/M	40	10×10	II	Moderate	Moderate	Minimal; lamellated interrupted
3	73/F	40	20×5	II	Minor	Minor	Minor; solid undulating
4	72/F	40	15×10	I	Minor	Minor	Prominent; lamellated interrupted
5	77/M	40	13×12	II	Very large	Moderate	Minimal; lamellated interrupted
6	71/M	60	7×6×4	II	Large	Large	Minimal; lamellated interrupted
7	81/F	60	16×14	I	Very large	Large	Prominent; solid undulating
8	71/F	30	20×15	II	Massive	Large	Prominent; solid and lamellated
9	79/M	40	10	I	Minor	Minor	Minimal; lamellated
10	63/F	25	29×13	III	Very large	Very Large	Extensive; combined spiculated and lamellated
11	74/F	14	32	II	Very large	Very Large	Minor; solid and lamellated
12	70/M	25	15×12	II	Very large	Very Large	Minor; solid and lamellated
13	76/M	50	16×14	II	Minor	Moderate	Moderate; solid undulating
14	73/M	25	20×20	I	Minor	Large	Moderate; solid and spiculated
15	48/M	24	17×10	I	Minor	Massive	Continuous; lamellated
16	75/M	7	15×10	II	Minor	Moderate	Moderate; linear interrupted
17	69/F	20	20	I	Minor	Moderate	Moderate; lamellated interrupted
18	75/F	50	20×12	II	Massive	Huge	Moderate; lamellated interrupted
19	82/F	66	10×12	III	Moderate	Moderate	Moderate; lamellated interrupted
20	79/M	40	15×10	III	Moderate	Moderate	Minor; solid undulating
21	60/F	28	12×15	III	Very large	Large	Minor; lamellated interrupted

All the ulcers were large. The largest measured 29×13 cm and involved the whole circumference of the leg.

The radiological findings are summarized in Table 2 A soft tissue mass was present in all the patients, and was very large in five and massive in one. Bone destruction was present to some degree in almost all patients, being extensive and massive in 11 patients. Only in one patient was there no visible bone destruction, and this was due to poor-quality radiographs. The bone destruction penetrated the periosteum and cortex. In eight cases it extended into the medullary cavity.

The periosteal reaction was lamellated in 13 cases, but in four a solid undulating reaction was still present when the bone destruction was not massive. Periosteal reaction was prominent in 11 cases and in these it was of the interrupted lamellar type. In one patient there was very dramatic spiculated periosteal reaction.

Histologically the tumors were low grade in seven patients, of moderate grade in 10 and high grade in only one.

The patients readily accepted amputation because of the discomfort they experienced. Partial resection was attempted in one patient but this was unsuccessful and amputation followed quite soon thereafter. Two patients, however, refused surgery and were lost to follow-up. There were two cardiac deaths, two patients died from sepsis and one from metastatic disease. All three sarcoma patients rapidly died. The rest of the patients did well, accepted a prosthesis and are free of disease. Because of the age of these patients they are likely to die from causes other than their cancer.

Case reports

Case 1 (no. 6 in Table 2)

A 71-year-old-man had been severely burnt on the upper left leg 60 years earlier. Six years previously he developed an ulcer associated with pain. Over the previous 6 months this had progressively increased in size.

On examination he was found to have an ulcer which was 7.5×6.0 cm in size, deep and involving bone. There was also intense scarring of the skin from the burn many years earlier. Radiographs revealed deep erosion of the upper tibia. MRI (Fig. 1) demonstrated a soft tissue mass on sagittal T1-weghted sequences showing a mass of intermediate signal.

The amputation specimen confirmed the deep extent of destruction found on MRI; the ulcer measured 4 cm in depth. There was no vascular invasion but deep destruction of the tibia.

Following his above-knee amputation the patient was fitted with a prosthesis and is free of disease 2 years later.

Case 2 (no. 18 in Table 2)

A 75-year-old-woman developed an ulcer in her right mid-leg 50 years previously. No history of trauma or infection could be obtained. The ulcer healed spontaneously and she was left with extensive scarring. Six months prior to referral she again ulcerated and developed a bulky mass

Fig. 1A, B Case 1. MRI of the upper tibia. **A** Sagittal T1-weighted (TR 300 / TE 16) sequence after Gd-DTPA demonstrates a moderate-sized soft tissue mass which extends from the surface, eroding the upper tibia and extending into the marrow cavity. The tumor showed no enhancement when compared with sequences prior to Gd-DTPA. **B** Axial T1-weighted (TR 300 / TE 16 23) sequence through the upper leg demonstrates destruction of the anterior cortex of the tibia. The tumor extends into the marrow cavity. There is fatty atrophy of muscles in the upper leg
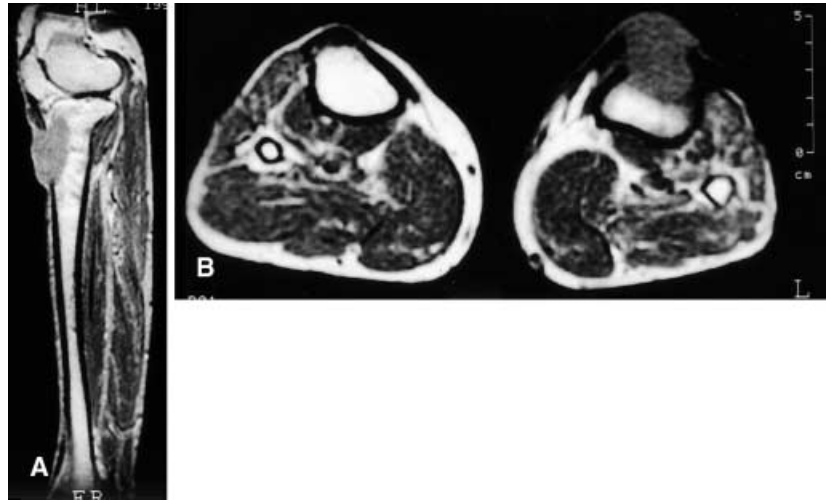

Fig. 2A–D Case 2. **A** Radiographs demonstrate a very bulky mass in the middle third of the leg. Extensive destruction of the tibia with associated posterior angulation is noted. The fibula appears to be free of disease. **B** Coronal T1-weighted image (TR 500 / TE 18) demonstrates an extensive ulcerating mass of intermediate signal intensity which infiltrates the muscle and fatty tissue in the anteromedial portion of the middle third of the leg. There is spread to adjacent areas of the diaphysis. **C** Sagittal T1-weighted image (TR 300 / TE 16) shows extensive involvement of the tibia with posterior angulation. **D** Axial T1-weighted image (TR 400 / TE 23) shows extensive destruction of the medial third of the tibia with an intimate relationship of the mass with the fibula. The fatty atrophy of the musculature in the posterior aspect of the leg is well demonstrated

involving the mid-portion of her leg. It grew rapidly and eventually involved the circumference of the mid-leg.

The ulcer measured 12 cm in length. On examination the mass was 16×20 cm, involving the entire circumference of the leg.

Radiographs (Fig. 2A) revealed the very bulky mass. There was posterior angulation of the tibia. A fracture of the tibia was also noted. MRI (Fig. 2B–D) in the axial, coronal and sagittal planes using T1-weighted sequences without gadolinium show extensive invasion of the tibia

by tumor. The amputation specimen showed a normal fibula despite the overlying mass in close proximity.

The patient underwent an above-knee amputation. The mass was 3 cm in thickness in the specimen. She was fitted with a prosthesis and is free of disease 15 months later.

Discussion

Malignancies that arise in chronic venous ulcers, scars or sinuses are referred to as Marjolin's ulcer. Marjolin [7], however, did not identify the warty ulcers he described as malignant. It was Dupuytren [8] who some 2 years later noted that these lesions were cancerous. The eponym was bestowed by Da Costa [9] in 1903. Marjolin's ulcer no longer refers only to carcinomas secondary to burns.

The commonest malignancy in this group of patients is squamous cell carcinoma, but more rarely basal cell carcinomas are found. These may frequently be multiple in the floor of an ulcer. To exclude a primary cancer as the cause of an ulcer there must be a minimum duration of the lesion, which Tenopyr and Silverman [10] set at 3 years. Most authors use this period but Yang et al. [11] and others have set this period at 1 month. It is therefore not surprising that of the 43 patients who were found to have malignant lesions of the leg in their study, 75% were basal cell carcinomas and only 25% squamous cell carcinomas. None of our 21 patients had basal cell carcinomas [12].

In addition to scars of various types and chronic venous ulcer, chronic osteomyelitis of the tibia with a draining sinus is a well-known precursor of squamous cell carcinoma [13]. Vishniavsky [14] collected up to 112 patients prior to 1996 and Fitzgerald et al. [15] reported on 23 such patients who were treated at the Mayo Clinic. There are frequent other reports but usually of only small numbers from any single center [16, 17, 18].

Three sarcomas were not included in the Mayo Clinic report – $^3/_4$ myeloma, reticulum cell sarcoma and fibroblastic osteogenic sarcoma. Only one of the patients in this study had preceding chronic osteomyelitis. Here the chronic osteomyelitis followed a chronic ulcer of many years' duration and the resultant malignancy was osteosarcoma. Although sarcomas [19] are well documented as following chronic ulceration of the leg their numbers are small compared with squamous cell carcinoma. The most common are fibrosarcoma [20] and malignant fibrous histiocytoma [21], angiosarcoma [22, 23], liposarcoma and leiomyosarcoma [24], while even parosteal osteosarcoma has been recorded.

Tropical ulcers are common in Africa, the West Indies and Asia. They occur in Brazil but are limited to the rural parts of the north and northeast of the country [25, 26, 27, 28, 29, 30]. The ulcers commonly contain *B. fusiformis* and *B. vicentii*, but these organisms are commonly found in the mouths of patients with carious teeth. The ulcer-osteoma which is so commonly seen in patients with tropical ulcer was not encountered in any of the patients in this study.

Ulcer-osteoma was first described in patients with tropical ulcer from West Africa. It is due to the heaping up of periosteum and associated subperiosteal sclerosis resulting in a knob-like mass protruding from the bony surface. In its most developed form it is only rarely seen in other conditions. In a recent study, however, the term ulcer-osteoma was used in a small series of patients with sickle cell anemia, intravenous drug abuse, peripheral vascular disease and neurological impairment [29].

A review of squamous cell carcinoma of the skin of all sites from Nigeria [31] revealed that only 54% were in the limb secondary to chronic ulceration of the legs, whereas in Uganda, squamous cell carcinoma of the legs accounted for 80% of cases, due to the much higher incidence of chronic leg ulcers in that country.

Fletcher [32], in reviewing a group of 720 soft tissue sarcomas from Malawi, found eight sarcomas that were presumed to have arisen in chronic ulcers (tropical). The list of possible etiologies of leg ulcers is long, although most result from venous insufficiency, arterial insufficiency and neuropathy.

A large variety of tropical diseases need to be considered, such as leishmaniasis, leprosy, sickle cell disease or syphilis. None of the patients in this study suffered from any of these diseases. A detailed history and physical examination usually provide the information needed to classify the leg ulcer into one of these groups.

Nine of the patients in this study appeared definitely to have venous ulcer. Historically [33] there has been doubt as to whether venous ulcers cause malignancy, because of the rarity of cancer in venous ulcer. Some have even suggested that skin cancer is no more common in venous leg ulcer than in other parts of the legs [34]. The rarity has been emphasized by one report which indicated only three malignant ulcers in 2000 lower limb venous ulcers [35] and another of five malignancies in 25 years of practice [36]. However, a detailed epidemiological study from Sweden [37] in which 11,000 patients with venous ulcers were matched with 33 patients from the Swedish Cancer Registry with squamous cell carcinoma, the relative risk of cancer was calculated at 5.80 and the median interval before development of the cancer was 25 years. The authors conclude that squamous cell cancer is a complication of chronic venous ulceration although the risk is small.

Bone destruction is the most important radiological finding for the surgeon. It was found in every patient who underwent amputation. In only one patient was it not seen on the radiographs, and this was due to the suboptimal quality of the radiographs. The most valuable study in these patients was MRI. It demonstrated the margins of destruction and the extent very well. It was also better than CT at demonstrating the soft tissue mass.

Unfortunately the periosteal reaction is poorly imaged on MRI. However, the periosteal reaction was not important for the diagnosis of malignancy. It was present to some degree in all patients but the type and extent bore no relationship to the size and etiology of the ulcer.

Patients with chronic ulcers from whatever cause need many biopsies of the margins to exclude malignancy. Nunnery et al. [24] have emphasized that sarcomas may arise in the center of an ulcer and that central biopsy should also be performed. Our patient with osteosarcoma demonstrated such a central growth.

The precise mechanism whereby chronic ulcers (wounds) develop malignancy is not certain, but chronic irritation and infection with resulting degeneration and regeneration may be instrumental in malignant transformation of either an epithelial or sarcomatous type [38]. Treves and Pack [39] have suggested that decreased vascularity and a weakened epithelium are unable to withstand the effects of carcinogens which are found in the wound itself. Ouahes et al. [40] have suggested from their studies that elevated expression of proto-oncogenes may be partly responsible for the increase in susceptibility of chronic wounds to malignant transformation.

Conclusion

Chronic ulceration of legs is a world-wide disease, but it is only in developing countries that ulcers are neglected for so many years that they eventually develop malignancy. The mean duration of the ulcers in this group was 36 years. All chronic ulcers that fail to heal need biopsies at regular intervals if the limbs are to be saved.

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