Granuloma multiforme is a skin disease of unknown cause that clinically resembles tuberculoid leprosy and granuloma annulare. Until now the disease has been reported only from Nigeria and Kenya. Here we present clinical and histopathologic findings in a patient with granuloma multiforme from Congo (Kinshasa).

The disease was first described by Leiker et al. (4) in 1964 after a detailed study of several hundred patients detected in various leprosaria in the Mkar area of northern Nigeria. Subsequently Browne (2) discovered 20 patients with granuloma multiforme among 400 being treated for leprosy in neighboring eastern Nigeria. More recently Leiker and Zeches des Plantes (1) and Verhagen et al. (5) have observed granuloma multiforme in Kenya.

Granuloma multiforme is a skin disease of unknown cause that clinically resembles tuberculoid leprosy and granuloma annulare. Until now the disease has been reported only from Nigeria and Kenya. Here we present clinical and histopathologic findings in a patient with granuloma multiforme from Congo (Kinshasa).

The disease was first described by Leiker et al. (4) in 1964 after a detailed study of several hundred patients detected in various leprosaria in the Mkar area of northern Nigeria. Subsequently Browne (2) discovered 20 patients with granuloma multiforme among 400 being treated for leprosy in neighboring eastern Nigeria. More recently Leiker and Zeches des Plantes (1) and Verhagen et al. (5) have observed granuloma multiforme in Kenya.

Clinically granuloma multiforme, tuberculoid leprosy, and granuloma annulare have a number of similarities: (1) the lesions are usually few; (2) they develop slowly, and (3) plaques expand peripherally while their centers become hard and resolve, producing a circinate pattern. Histopathologically, granuloma annulare and granuloma multiforme are similar, but tuberculoid leprosy has distinctive features. Histologic characteristics of the three diseases are listed in Table 1.

REPORT OF A CASE

A 45 year old Congolese man of the Baluba tribe was examined in May 1967 during a survey of 200 patients under treatment for leprosy at the Kellersberger Memorial Hospital, Bibanga, Kasai Province, Congo. He stated that his deceased father had had leprosy. He was a lifelong resident of this area, which is about 60 miles east of the town of Mbuji Mayi. The region is hilly savannah, with sandy soil, and has distinct wet and dry seasons.

Clinical findings. In 1960 the patient noted pruritic papules where well-developed lesions were found on examination—left deltoid, right forearm, right lumbar, and sacral areas. These papules had
A chest roentgenogram revealed no pulmonary infiltrates; 1 percent eosinophils.

Routine urine and stool examinations and a hemoglobin was 13.5 gm./j.

White blood cell count was 8,300/cumm, with a distribution of 71 percent neutrophils, 28 percent lymphocytes, and 1 percent eosinophils.

Skin scrapings revealed no fungi. Hemoglobin was 13.5 gm./100 ml, and the white blood cell count was 8,300/cumm, with a distribution of 71 per cent polymorphonuclear neutrophils, 28 per cent lymphocytes, and 1 per cent eosinophils. Routine urine and stool examinations and a chest roentgenogram revealed no abnormalities.

The intracutaneous injection of 0.1 ml. lepromin (Wade modification of the Mitsuda-Hayashi lepromin) produced an area 4 mm. wide after 48 hours (Fernandez reaction) and 7 mm. wide after 30 days (Mitsuda reaction).

The patient had taken DDS by mouth (300 mg. twice a week) for 30 months, without improvement.

A biopsy specimen was taken from the elevated edge of a lesion in the lumbar region and fixed in cold 10 per cent formalin. The specimen included a margin of normal skin.

**Histopathologic findings**

The fixed biopsy specimen was blocked in paraffin, cut at 5 microns, and stained by a combined trichrome-Fite-Faraco (TRIFF) method. Later, additional sections were cut, and a variety of other stains were made. These included hematoxylin-cosin; Fite-Faraco for acid-fast bacilli; Movat’s pentachrome for elastica, mucin, and collagen; periodic acid-Schiff; Gomori: reticulin; Brown and Brenn for bacteria; and Warthin-Starry for spirochetes.

Granulomas were prominent within the panniculus carnosus but were also found in lipo-dermal areas as well. Some granulomas were noted in the bladder and skin adnexa.

**Clinical**

<table>
<thead>
<tr>
<th>Granuloma annulare</th>
<th>Tuberculoi leprosy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually hands and feet involved.</td>
<td>Usually hands and feet involved.</td>
</tr>
<tr>
<td>No sensory loss or nerve enlargement.</td>
<td>No sensory loss or nerve enlargement.</td>
</tr>
<tr>
<td>Foci of collagen degeneration surrounded by a granulomatous zone.</td>
<td>Granulomas may involve all layers of dermis.</td>
</tr>
<tr>
<td>Nerves intact.</td>
<td>Nerves damaged.</td>
</tr>
</tbody>
</table>

**Histopathologic**

<table>
<thead>
<tr>
<th>Granuloma annulare</th>
<th>Tuberculoi leprosy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random distribution of granulomas in dermis, but papillary layer spared. Plasma cells, mast cells, and eosinophils sometimes present.</td>
<td>Granulomas may involve all layers of dermis.</td>
</tr>
<tr>
<td>Nerves intact.</td>
<td>Nerves damaged.</td>
</tr>
<tr>
<td>Granulomas may involve all layers of dermis.</td>
<td>Nerves damaged.</td>
</tr>
</tbody>
</table>

**Response to therapy**

- No response to dinitrochlorobenzene. Lesions persist for years and eventually heal spontaneously.
- May resolve spontaneously or may respond to local steroids.
- Tend to be self-healing, but healing hastened by DDS.
Lesions of the left deltoid and right lumbar regions are shown. The lesions have raised serpiginous margins which surround a broad slightly indurated and slightly hypopigmented central zone. (AFIP neg. 69-3643).

Lesion on the left arm. It has a smooth lower margin and a serpiginous margin above. (AFIP neg. 69-3645).
The granulomas were not circumscripted, and merged with surrounding dermal collagen. They were composed of epithelioid cells, histiocytes, and Langhans' giant cells and contained a few plasma cells, mast cells eosinophilic leukocytes, and lymphocytes (Fig. 5). Reticulum and collagen fibers traversed the granulomas. No definite evidence of degeneration of collagen fibers was seen. The collagen fibers were not tinctorially altered, nor had they lost their normal birefringence. Between the granulomas, and distinct from them, were scattered collections of plasma cells, especially in the loose connective tissue around the dermal appendages, vessels, and nerves (Fig. 8). Dermal elastica was strikingly reduced within the lesion, and each of the granulomas contained minute fragments of phagocytosed elastic fibers. Both histiocytes and giant cells contained fragments of elastica (Fig 3, bottom left and right), and some of the phagocytosed fragments were surrounded by acid mucosaccharide. Surviving elastic fibers were few, as there were only scattered fragments between bundles of dermal collagen, and these were surrounded by histiocytes. None of the granulomas contained areas of necrosis, foreign bodies, or microorganisms.

COMMENT

Granuloma multiforme has been reported only from central Africa, and the patient here described is the first reported from south of the equatorial forest of central Africa. Personal experience (W.M.M.) indicates that granuloma multiforme is uncommon in Congo. No case has yet been found in the lower Congo or North Kivu areas (in the Ituri forest) among patients being treated for leprosy, and our patient was the only one found among 200 patients at a single location in the Kasai Province. Additional surveys are essential to determine the prevalence and distribution of granuloma multiforme in Congo.

The cause of granuloma multiforme is not known. No microorganisms have been seen in the lesions, but cultures for bacteria and viruses have not been done. An inflammatory or allergic response to insect bites or stings has been suggested (1,4). Verhagen et al. (7) believe that granuloma multiforme may be a variant of granuloma annulare, atypical forms of which have been described following bites by the gnat Culicoides furcatus in the Canal Zone (8), Culicoides sp. are widely distributed throughout central Africa, but there is at present no direct evidence to implicate this or any other insect.

Marshall et al. (3) in a detailed study of the clinical, pathologic, and geographic aspects of 30 patients, noted a conspicuous degeneration of connective tissue, especially the collagen. Allenby and Wilson Jones (5), however, found reduced elastica in four of 15 biopsy specimens and noted giant cells that appeared to be engaged in phagocytosis of elastic remnants. They suggest that granuloma multiforme is identical with necrobiosis lipoidica diabetica. In our patient, the granulomas appear to

Fig. 3. Top. This is through the margin of the lesion. The inflammatory cell infiltrate in the dermis has raised the overlying epidermis. Elastic fibers, stained black, have a normal distribution in the uninvolved dermis seen at the bottom and at the right side of the picture. Elastic fibers are greatly reduced within the lesion and most of those that remain are fragmented and lie within histiocytes and giant cells. (M)ovat stain X70, AFIP photo No. 70-3331.

Bottom left. At the margin of the lesion there is active phagocytosis of elastica. Elastic fibers are fragmented and here three strands of elastica are within a giant cell. (Movat stain X455, AFIP photo No. 70-3331).

Bottom right. This granuloma is composed of epithelioid cells and two giant cells, both of which contain fragments of elastica. (Movat stain X350, AFIP photo No. 70-3332).
FIG. 4. Section through the area of maximum cellular reaction. There are granulomas in the upper, middle, and lower dermis. Chronic inflammatory cells, mainly plasma cells, are scattered throughout the dermal collagen, especially around the small vessels. The granuloma in the outlined area is enlarged in Figure 5. (TRIFF, X250, AFIP neg. 69-4138-1).

FIG. 5. A granuloma in the lower dermis. It shows a giant cell surrounded by a mixture of epithelioid cells and fibroblasts. It contains a few strands of collagen. (TRIFF, X250, AFIP neg. 69-4138-1).
be a manifestation of the phagocytosis of dermal elastica because the giant cells and histiocytes in each granuloma contained elastic fibers. Whether this reflects a primary degeneration of elastica, or is secondary to an obscure process, cannot be determined, but the focal nature of the disease, its tendency to spontaneous resolution, and the fact that phagocytosis of elastica was not a constant feature in the study by Allenby and Wilson Jones (1), all argue against granuloma multiforme being a primary degeneration of elastica.

The diagnosis of granuloma multiforme requires an evaluation of the clinical and histopathologic findings, as well as a careful search for microorganisms to exclude the common infectious granulomas of the skin. Tuberculoid leprosy, in particular, can be excluded only after clinical evaluation has failed to demonstrate anesthesia of the lesion, and histopathologic study has failed to reveal inflammatory changes of dermal nerves and failed also to reveal acid-fast bacilli within nerves. The demonstration of fragmentation and phagocytosis of elastica is another feature which may be helpful in the diagnosis of granuloma multiforme. Clarification of the cause and pathogenesis of granuloma multiforme awaits further clinical and pathologic studies.

SUMMARY

This is the first report of a Congolese with granuloma multiforme, a disease entity which has been recognized only in tropical Africa. The patient described is a 45 year old man from Kasai Province of Congo (Kinshasa), who had gradually enlarging macules of the forearms, as well as on the lumbar, deltoid and sacral regions. The lesions had elevated circinate borders, in-

Fig. 6. There is an intact nerve (arrow) in the deep corium which, although surrounded by plasma cells, is not structurally altered. Langhans' giant cells are evident in a nearby granuloma. (TRIPP, X304, AFIP neg. 69-2678).
The margins of the lesion. Granulomas were
reduction of elastic within the lesion and
active phagocytosis of dermal elastic at
the margin of the lesion. Granulomas were
comprising of giant cells, histiocytes
and epithelioid cells, containing phagocy-
tosed elastic fibers. The cause of the frag-
mentation and phagocytosis of elastic is
unknown. It may be a reaction to a primary
degeneration of elastic or it may be sec-
dary to an obscure antecedent injury.

The diagnosis of granuloma multiforme
depends on a careful clinical and histopatho-
logic evaluation. Tuberculoid leprosy can be
excluded only after clinical studies have
failed to reveal anesthetic of the lesions
and histopathologic studies have failed to
reveal inflammatory changes of dermal
nerves or acid-fast bacilli in dermal nerves.

RESUMEN

Esta es la primera vez que se describe un caso
de un Congolese con granuloma multiforme,
enfermedad que ha sido diagnosticado solamente en África tropical. El paciente es un hombre de 45 años de la Provincia de Kasai del Congo (Kinsona), que presentaba nódulos que aumenta-
ban gradualmente de tamaño, en el antebrazo y en las regiones lumbares, deltoideas y sacras. Las lesiones tenían bordes circinados elevados, centros indurados y no eran anestésicas. En el momento del diagnóstico el paciente estaba en tratamiento antileproso en un leprocomio. Histopatológicamente, había una marcada re-
ducción de la elástica dentro de la lesión y una fagocitosis activa de las fibras elásticas en el mar 
gen de la lesión. Los granulomas eran con-
spicuos en todo el dermis. Estaban formados de células gigantes, histiocitos y células epitelioide, que contenían fibras elásticas fagocitadas. La causa de la fragmentación y fagocitosis de la elástica es desconocida. Puede ser una reacción a una degeneración primaria de la elástica o puede ser secundaria a un antecedente de infección no determinado.

El diagnóstico de granuloma multiforme
depende de una cuidadosa evaluación clínica e
histopatológica. La lepra tuberculoi de se puede
excluir solamente después que los estudios clí-
nicos han demostrado que no hay anestesia en
las lesiones y los estudios histopatológicos han
demostrado que no hay cambios inflamatorios o bacilos alcohol-acido resistentes en los nervios dérmicos.

RESUME

Ceci constitue le premier rapport, chez un
Congolais, de granulome multiforme, une entité
morbidité qui n’a été reconnue qu’en Afrique
tropicale. Le malade que l’on décrit est un homme âgé de 45 ans, originaire de la Province
du Kasai, en République Démocratique du Congo
(Kinsona). Ce malade présentait des macules qui s’étendaient progressivement sur l’avant-bras,
de même qu’aux niveaux des régions lombaire,
deltoïde et sacrée. Les lésions présentaient des
bords circinés surlevés, un centre induré, sans
anesthésie concomittante. Au moment du diag-
nostic, le malade était en traitement pour la
lèpre dans une lépreserie. Du point de vue
histopathologique, on a noté une réduction
notable des fibres élastiques à l’intérieur de la
lésion, ainsi qu’une phagocytose active des
fibres élastiques du derme à la périphérie de
la lésion. Les granulomes pouvaient facilement
être vus à travers le derme. Ils étaient con-
stituits de cellules géantes, d’histiocytes et de
cellules épithélioides, contenant des fibres éla-
tiques phagocytées. La cause de cette fragmenta-
tion, de même que la cause de la phagocytose des
fibres élastiques, reste non élucidée. Il peut
s’agir d’une réaction à une dégénérescence
primitive des fibres élastiques, ou bien ces
lésions pourraient être secondaires à un trauma-
tisme antérieur méconnu.

Le diagnostic du granulome multiforme pro-
cède d’une évaluation clinique et histopatolo-
rique soigneuse. La lèpre tuberculoi de ne peut
être exclue qu’après que les études cliniques
n’ont pas permis de mettre en évidence une
anesthésie au niveau des lésions, et à la condi-
tion que les études histopathologiques n’ont
pas réussi à révéler des modifications inflam-
matoires au niveau des nerfs du derme ou la
présence de bécaties acid résistants chez les
nerveux du derme.

Acknowledgments. A histopathologic diag-
nosis of granuloma multiforme in this case was
made on a biopsy specimen by Dr. E. Wilson
Jones of St. John’s Hospital, London, and
Dr. D. J. Harman of the Leprosy Study Centre,
London. Dr. D. L. Leiker reviewed histopatho-
logic sections, and Dr. C. H. Binford made
helpful suggestions. Figures 4-6 illustrate areas
in a section prepared by the Leprosy Study
Centre (there Lab. No. 8621).

This study was supported in part by Ameri-
can Leprosy Missions, Inc., New York; in part
REFERENCES