ONCHOCERCAL DERMATITIS-CURRENT CONCEPTS OF PATHOGENESIS

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Onchocerciasis, once thought to be a rare and unimportant disease, has emerged since World War II as one of the world's most important public health problems, afflicting an estimated forty million people. There are endemic areas throughout Tropical Africa, in the Yemen Arab Republic, Mexico, Guatemala, Venezuela, and recently recognized foci in Colombia and Brazil. Onchocerciasis presents an endless variety of clinicopathologic features. The organs most severely involved are skin, lymph nodes, and eye. Because these "target" organs are superficial, the physician has unique opportunities to study pathogenesis and to monitor the effects of treatment. Thus, among all filarial infections of man, onchocerciasis presents unique opportunities to study pathogenesis, hostparasite relationships, effects of treatment, and to serve as a basis of comparison with bancroftian and other filarial infections.

Classically, onchocerciasis has three cardinal features: (1) subcutaneous nodules which contain adult worms; (2) interstitial keratitis which may progress to blindness; and (3) chronic dermatitis. Adult worms are up to 50 cms long and provoke an inflammatory reaction which leads to fibrous encapsulation. These nodules usually form over bony promi-Microscopically the adult worms nences. can be identified as filariae by their general features and specifically by regularly spaced annulations which are about 70 microns apart at midbody. Another helpful specific feature is the presence of regularly spaced striae, two per annulation, seen clearly with the PAS stain.

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A nodule may contain one or more gravid female worms; nongravid worms and male worms may or may not be present. Most nodules, however, contain multiple worms which are intertwined. Within each nodule the inflammatory reaction varies from suppurative and granulomatous through stages of granulation tissue to fibrosis, sometimes with focal mineralization, osseous metaplasia, and cholesterol deposition. Of special interest is the thin layer of "fibrinoid" on the cuticle of many segments of the adult worm. This layer resembles the Splendore-Hoeppli phenomenon and probably is immune complex. Collections of neutrophils collect near this layer and destroy it. The nodule's outer layer of hyalinized scar incarcerates the adult worms and prevents them from doing direct harm. Their progeny (microfilariae), however, escape from the nodules and migrate widely.

Microfilariae of *O. volvulus* are readily identified by specific features which include size and the nuclear configurations of caudal and cephalic ends. Most microfilariae lie free in the tissues, are numerous in the dermal collagen, cornea, and lymph nodes, but have also been identified in blood, lymphatics, spinal fluid, urine, kidney, sputum, lung, liver, and pancreas.

The first subjective manifestation of onchocercal dermatitis is intermittent pruritus. This becomes more severe and more persistent as the dermatitis becomes more severe to the point where it prevents sleep and productive work. Clinically, there are a number of objective changes (Figs. 1 - 12).

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Fig. 1—Onchocercal dermatitis with altered pigmentation - hyperpigmented macules alternating with areas of hypopigmentation.



Fig. 2—Multiple papules on the forearm also known as gale filarienne (filarial scabies).

Hyperpigmentation is an early sign and is characterized microscopically by thickening of the epidermis and keratin, thus increasing the thickness of the pigmented layer without an increase in the concentration of melanin in the epidermis.

Hypopigmented macules also a characteristic feature of onchocercal dermatitis are characterized by decreased melanin in the basal



Fig. 3—A long standing onchocercal dermatitis. The right leg is oedematous from sclerosing lymphadenitis. In addition the skin of the left leg shows spotty depigmentation. This is sometimes called "leopard skin".



Fig. 4 — Onchocercal dermatitis showing a characteristic intraepidermal abscess. Microfilariae migrate into the epidermis, especially after treatment with diethylcarbamazine and provoke intraepidermal collections of polymorphonuclear neutrophils. Note the microfilaria within the intraepidermal abscess. H & E x 250.

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Fig. 5 — Microfilariae of O. volvulus which degenerate in the dermis provoke a variety of inflammatory reactions. Here histiocytes, epithelioid cells and giant cells have formed around a degenerating microfilaria. H&E x 375.



Fig. 6—Dermal fibrosis is a common feature of onchocerciasis. Here large, fibroblasts are present within the dermis. H&E x 600.

layer, and also by an accumulation of melanin in phagocytic cells in the dermis. Lesions of tuberculoid leprosy, granuloma multiforme, tinea versicolor, and streptocerciasis must be considered and excluded by careful clinical and pathological study.

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Fig. 7 — The adults of Onchocerca volvulus live innodules within the deep dermis and subcutaneous tissue. Sections of these reveal adult male and female worms coiled and intertwined together. They are surrounded by hyalinized scar tissue which incarcerates them preventing their migration. The gravid females elaborate microfilariae which pass through the scar tissue and enter skin, eye and lymph nodes and other organs, where they provoke inflammatory reactions, fibrosis and other destructive lesions. H&E x 8.2.

Oedema of the skin, usually a feature of heavy infections is an accumulation of acid mucosaccharide between collagen fibers. Associated changes are marked tortuosity of dermal vessels and dilated dermal lymphatics.

Leopard skin distinct from the hypopigmented macules is white (depigmented) skin interrupted by a polka-dot arrangement of sharply defined black spots around the openings of sweat glands and hair folicles. Leo-



Fig. 8 — A detailed view of a single cross section of a degenerating adult Onchocerca volvulus. It is surrounded by eosinophilic hyaline material which resembles the material of the Splendore-Hoeppli phenomenon and is probably immune complex. A portion of it has been dissolved by polymorphonuclear neutrophils, possibly by fibrinolycins and other enzymes released by the neutrophils. X 145.



Fig. 9 — Microfilariae of Onchocerca volvulus tend to concentrate in the upper dermis, especially in the dermal papillae. Here they are available to the bite of the vector simulidae. H&E x 440.

pard skin is most common on the skin over the shin, but also involves the skin of the inguinal region, labia, penis, scrotum, and axil-



Fig. 10—In onchocercal dermatitis scar tissue gradually replaces the elastic fibers of the upper dermis. Note the layer of scar tissue which has replaced the normal dermis containing elastic fibers. Movat stain x 110.



Fig. 11—End stage onchocercal dermatitis. The epidermis is thin and atrophic and the normal cermal collagen is replaced by hyalinized scar tissue some of which is oriented about tortuous vessels within the dermis. Two microfilariae are in this section.

lary folds. Microfilariae are scarce in the depigmented skin but usually numerous in adjacent pigmented skin. Leopard skin is a feature of longstanding onchocercal dermailtis.

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Fig. 12—Lymph nodes from patients with onchocerciasis showing a variety of characteristic features including melanin pigment deposited in the cortex from the chronic dermatitis and replacement of lymphoid tissue by fibrofatty elements, x 2.6.

Lizard skin also a feature of longstanding onchocercal dermatitis is characterized microscopically by atrophy of the epidermis and scaling of the keratin layer. The underlying dermis is not necessarily thickened or oedematous.

In elephant skin, another manifestation of longstanding onchocercal dermatitis the skin hangs in loose folds usually from thigh and knee. Microscopically the epidermis is atrophic, as in lizard skin, but the dermis is thickened and organized by layers of reticulum and scar tissue which has a concentric pattern around tortuous dermal vessels. Much of the perivascular scar tissue has a "fibrinoid" appearance which we believe is immune complex.

Gale filarienne or filarial scabies is papular dermatitis and usually seen on the trunk, thighs, or arms. The papules tend to come in crops and are associated with intense pruritus. Microscopic study reveals intra-epidermal abscesses, each a reaction to a microfilaria of *O. volvulus* which has migrated into the epidermis.

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Lymphadenitis, inguinal and femoral nodes are most commonly involved. Clinically the nodes are slightly enlarged, firm, discrete, freely movable, and not tender. Clusters of involved nodes lie deep to hanging groins. These pouch-like folds of redundant tissue, also called adenolymphoceles, hang from one or more clusters of involved inguinal or femoral nodes. Sometimes all four quadrants are involved. Grossly the nodes are scarred and focally pigmented. Microscopically the nodes progress through a series of changes from early sinus histiocytosis and depletion of lymphoid follicles, through fibrous thickening of capsule and trabeculae to the end stage characterized by almost complete replacement by hyalinized scar tissue. As scar tissue increases, it assumes a stricking perivascular arrangement. Special stains reveal deposits of protein which by histochemical staining and appearance is immune complex. How this immune complex forms is unknown. But its perivascular and concentric orientation suggests that microfilarial antigens released in the tissues meet and combine with circulating antibodies diffusing through the walls of blood vessels. The "end stage" lymph node has characteristic features. Not only is lymphoid tissue replaced by scar, but lymphatics are dilated, plasma cells and eosinophils are numerous, and varying numbers, of microfilariae lie between the collagen fibers.

Elephantiasis, elephantoid swellings of legs and genitalia have been associated with onchocerciasis in the Oubangi region of Zaire since the early 1900s. This suggests that onchocerciasis involves the deep lymph nodes as well as the superficial lymph nodes. To date, however, deep lymph nodes have not been studied nor have modern techniques been used to exclude infection by *Wuchereria bancrofti* in these patients.

Swoda, the name for the characteristic clinical picture of onchocercal dermatitis in the Yemen Arab Republic is derived from an Arabic word meaning dark or black. These patients have few nodules and few microfilariae but many papules, usually limited to one limb which is swollen and hyperpigmented. Diethylcarbamazine given by mouth produces a severe local reaction in these patients. In contrast to African patients, the regional nodes are very large, soft, and tender. According to medical lore in Yemen, the enlarged nodes are the "um" or mother of the disease. It is thus customary for local surgeons to excise the nodes. Microscopically the skin reveals a diffuse dermatitis characterized by intra-epidermal abscesses, massive numbers of lymphocytes, histiocytes, plasma cells, and eosinophils around the vessels, inflammatory mucin in the dermis, and very rare microfilariae. The lymph nodes unlike those from Africa with onchocerciasis have hyperplastic follicles, are not scarred, and contain no microfilariae.

Deep organ involvement: A recent autopsy on a Zairian revealed a nongravid female in the wall of the aorta. Another autopsy revealed large numbers of degenerating microfilariae in the renal glomeruli, in the liver, and in the lung. These were widespread, had provoked inflammatory reactions, and were lying within microabscesses. The most striking changes were in kidney (acute glomerulitis) and lung (multiple microabscesses). These probably caused the patients' death.

Emaciation: In hyperendemic areas occasional patients are encounted who have massive infection, little or no reaction to the parasite (anergy), and extreme emaciation. The reasons for the anergy and the emaciation have not been studied. Malnutrition, immunological defects, or other factors could play a role.

Effects of Diethylcarbamazine: Diethylcarbamazine (DEC) is an essentially perfect microfilaricide. It is taken by mouth, has no effect on noninfected subjects, but in those with onchocerciasis, rapidly kills microfilaria in the tissues. This produces a variety of acute reactions, including intense itching, prolonged and severe scratching with excoriation, erythema, swelling papules, tenderness, pain of lymph nodes, and sometimes fever, urticaria, cough, and collapse. Microscopic study reveals that microfilariae begin to degenerate in the skin a few minutes after taking DEC. Some are surrounded by eosinophils which progress to eosinophilic abscesses over a period of a few hours to a few days. Others provoke foreign body granulomas. Some microfilariae are thus trapped in the dermis but others migrate into the epidermis as if to escape the effects of the drug. Within the epidermis they may provoke intra-epidermal abscess or they may provoke no response and gain the keratin where they are eventually sloughed. Other microfilariae (sometimes massive numbers) migrate via the lymphatics to reach the lymph nodes. Here they degenerate forming subcapsular abscesses.

CONCLUSIONS

Studies on the pathogenesis of onchocerciasis have just begun. The opportunity to study immune mechanisms within the body is a biproduct of treatment. The mechanism by which DEC kills microfilariae in vivo is unknown and begs for simple and obvious studies. We know, for instance, that DEC has no direct effect on microfilariae in vitro even when the concentration is many times higher than that reached in tissues. Does onchocerciasis involve deep lymph nodes and cause elephantiasis in the Oubangi region? If so, why is this not a feature of onchocerciasis in other hyperendemic areas? Or is it? And, why are the clinical features of onchocerciasis so different from one geo-graphical area to another. These are some of the questions which we must now ask and try to answer.