EDEMA RESULTING FROM EXPERIMENTAL FILARIAISIS

D.S. Folse, A. Ewert

Departments of Pathology and Microbiology, University of Texas Medical Branch, Galveston, Texas, USA

ABSTRACT

Domestic cats and patas monkeys were infected with Brugia malayi so that the worms localized in the regional lymphatics of the hind legs. Reaction to the filarial parasites resulted in visible local edema in cats and disruption of normal lymph flow in the monkeys. Edematous tissue was examined grossly and by light and electron microscopy. Lymph flow patterns were examined by direct observation following injection of lymph staining dye and reflection of the skin, by X-ray following injection of radio-opaque contrast media, and by lymphoscintigraphy after subcutaneous injection of radioisotopes. Clinical edema occurred in cats but not in monkeys. However, disruption of normal lymph flow in monkeys infected with Brugia could be demonstrated by lymphoscintigraphy.

Lymphedema is an important component of many disorders. The precise details concerning production and transport of lymph in an area of the body damaged by injury or infection are not completely understood and are difficult to study. During experimental studies using cats and patas monkeys infected with Brugia malayi, an important parasitic infection in many tropical countries, we were frequently able to produce regional lymphedema (1). This permitted us to observe changes in the lymphatics during the onset and resolution of lymphedema. These observations are presented to suggest mechanisms for the initiation of lymphatic dysfunction and for the ultimate resolution of regional lymphedema.

METHODS, RESULTS AND DISCUSSION

Infected Brugia malayi dissected from vector mosquitoes were placed in a drop of saline over artificial puncture wounds on the hind feet of cats and monkeys. Within 24 hours, the larvae migrated to the periphery of the first intervening lymph node, the popliteal. As the parasites matured and increased in size, the vessels dilated, valves of the infected lymph vessels became incompetent, and the worms migrated down towards the site of infection on the hind foot. In cats, visible edema developed within a month of infection and persisted up to 3 months after the last infection. The contralateral uninfected hind legs remained normal in appearance.

Observations on more than 50 Brugia-infected cat legs showed progressive occlusion of the two major lymphatic vessels. Exudative inflammation, thrombosis, polypoid intimal ingrowths and eventually granulomatous inflammation, especially prominent around dead worms, was also seen in
the lymphatic walls (2). Thrombus formation occurred most commonly at valve sites and attachment to the intima could usually be demonstrated. Red blood cells were often seen within thrombi before organization with its ingrowth of capillaries into the thrombus had developed. Often inflamed lymphatic walls adjacent to thrombi contained capillaries in close proximity to the vessel lumen and it was evident that distortion of tissues resulting from adult worm movement or adjacent muscle contraction could have caused the red cell leakage seen in the lumen of some lymphatic vessels (Fig. 1).

Lymph vessel wall inflammation began with the accumulation of lymphocytes in the adventitial layer. Soon the cellular accumulation contained additional cell types including other white blood cells, fibroblasts, macrophages and especially mast cells. In chronic reinfected animals, eosinophiles were sometimes present in large numbers. The exact role of these various cells has not been adequately documented. As the inflammation increased, the lumen of the lymphatic vessel was compromised through accumulations of lymphocytes, by ingrowth of the intimal lining, or even frank infoldings of the vessel wall (Fig. 1), by thrombosis or any combination of these phenomena.

Injection of sky blue dye into the foot pad in the anesthetized animal five minutes before euthanasia made the lymph vessels clearly visible. In lymphatics of cats chronically infected with Brugia, the major vessels containing the dye were enlarged, distorted, tortuous, and firmly ropy. The presence of many small, pre-existing or newly formed, satellite vessels in infected
limbs was in sharp contrast to the appearance in non-infected legs in which lymph capillaries were not usually discernible or were few in number (Fig. 2). Examination of serial and step-cut sections suggested that vessels were not linearly contiguous but more lattice-like and thus less efficient than straight channels.

We postulate that edema produced in the Brugia-infected cat leg was removed primarily by dilated satellite vessels, aided by persistent slit-like communicating spaces of the compromised lumens of the major lymphatic vessels of the area. Additionally, new capillary lymphatics that connect existing vessels and that connect edematous tissue with patent lymph vessels also probably play a role in edema removal (Fig. 2).

Although the presence of adult worms and microfilaria demonstrated filarial development, no visible edema was produced in seven patas monkeys (Erythrocebus patas), even after repeated doses of 50 infective Brugia larvae. To determine if lymph flow had been altered by this subclinical infection, $^{99m}$Tc-sulfur colloid was inoculated into the interdigital space of the rear feet of anesthetized animals (4), positioned under a scintillation camera in such a way that the course of the lymphatics could be monitored. Counts were recorded continuously with accumulations noted every 10 minutes over a three-hour span. Some nuclide appeared in the popliteal node of the uninfected leg after 10 minutes but in the infected leg it pooled in tissue near the injection site where it remained for at least one hour. Between one and three hours post-inoculation, activity was detected in both the popliteal and inguinal lymph nodes in the normal limb but only in the inguinal node in the infected leg. The radionuclide in
the infected leg bypassed the popliteal node, indicating that in the monkey, normal lymph drainage was altered although edema was not evident. The microscopic appearance of lymphatic vessels resembled that from cats but tissue involvement was less severe.

CONCLUSIONS

Experimental *Brugia* infections were established in domestic cats and patas monkeys. Clinical edema occurred in cats but not in monkeys. In infected cats, lymph flow appeared to occur primarily through dilated satellite vessels. Although edema was not evident in infected monkeys, lymph flow alteration was demonstrated by lymphscintigraphy.

Many questions concerning the production and resolution of edema due to lymphatic filariasis remain to be investigated.

REFERENCES


Dean S. Folse, D.V.M., Ph.D.
Pathology
Keiller 114, F-09
University of Texas Medical Branch
Galveston, TX 77550 USA