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Research Note

CHRONIC CHAGASIC CARDIOPATHY: ROLE OF CD4 T CELLS IN THE ANTI HEART AUTOREACTIVITY

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American trypanosomiasis, a parasitic disease caused by the flagellate protozoon *Trypanosoma cruzi,* presently affects about twenty million people in the world (Tropical Disease Research Eight Programme Report 1985-1986. PNUD/Banque Mondiale/WHO, Geneve, 1987). During the course of this disease one can distinguish an acute and a chronic phases. The acute phase is characterized by the presence of the parasite in the peripheral blood as well as within several tissues including heart muscle. In contrast, during the chronic phase, which in humans may last for more than 20 years, parasites are virtually absent in the peripheral blood and tissues. Particularly in the heart multiple foci of mononuclear inflammatory infiltration and myocytolysis are frequently found although histopathological analysis of hearts rarely reveals parasites. (R. Ribeiro dos Santos et al., 1981. Chagas' disease, p. 115-134 In H. Schonfeld, *Antiparasitic chemotherapy*, S. Karger, Basel).

These data support the hypothesis of an autoimmune mechanism involved in the generation of myocytolysis (F. Kierszembaum, 1985. Is there autoimmunity in Chagas' disease? *Parasitol. Today, 1:* 4-8).

It was thus in this context, that we designed a number of experiments in order to determine which lymphocyte subset(s) was involved in the cytolysis of myocardial cells occurring in mice chronically infected by *T. cruzi.*

Firstly, we grafted into the ears of chronically-infected animals hearts obtained from newborn syngeneic donors. The grafts have never beaten, and were completely rejected and absorbed in 10-20 days. This was in striking contrast to those organs grafted into normal syngeneic recipients, which can persist and beat for more than one year (Figs A, B). The histopathological analysis of heart tissue grafted into chagasic mice revealed a persistent and intense mononuclear inflammatory infiltrate with eventual myocytolysis and heart tissue resorption, quite similar to the pattern obtained when hearts were transplanted in allogeneic conditions (Fig. C). Importantly, similar results were obtained varying both the mouse and the parasite strains.

Once established that heart grafts were rejected, we asked the question which T cell subset was involved in triggering this process. Thus, before grafting the heart tissues, chronically-infected animals were treated with anti-CD4 or anti-CD8 monoclonal antibodies (MAb). All animals receiving anti-CD8 MAb continued to reject the transplanted organs, whereas all anti-CD4 MAb treated animals failed to do so.

In addition, the histological pattern of the heart tissue as well as heart beats in these anti-CD4 treated mice, were comparable to those observed in hearts grafted into normal syngeneic recipients.

Lastly, we wondered whether T cells from chagasic animals were able to yield rejection of hearts transplanted into the ears of naive normal syngeneic recipients. We observed that injections of splenic T cells from chronically-infected mice did promote a severe inflammatory reaction adjacently and within the grafts. Again, this process could be blocked by treating the cells to be transfered with an anti-CD4 MAb but not with an anti-CD8.

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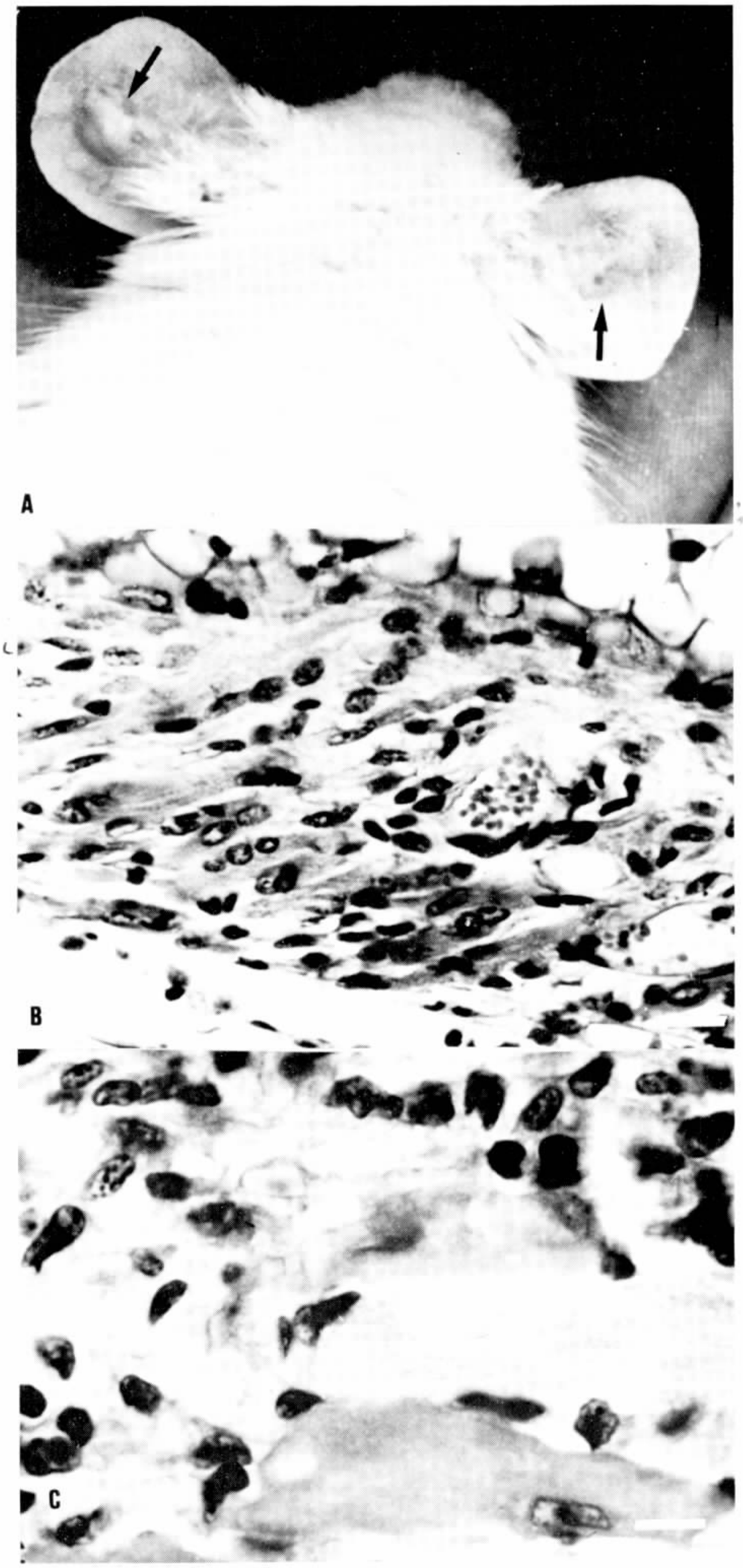

Syngeneic newborn-derived heart transplants in Balb/c mice. A: the external profile of grafts (arrows) two months after transplantation into the ears of a normal recipient. B: the corresponding histological pattern. C: myocytolysis together with a mononuclear cell infiltrate that corresponds to a heart tissue 10 days after being grafted into chronic chagasic recipient.
Bar = 35 μm (B) and 8 μm (C).

The data reported herein using the model of heart transplants into the ear lobes brought evidence showing that T cells, and particularly CD4-bearing lymphocytes, from *T. cruzi* chronically-infected mice are necessary for triggering the mechanism(s) eventually leading to the rejection of the syngeneic grafted cardiac tissue. This is in agreement to the data showing that the majority of T cells infiltrating the heart in both acute and chronic phases of experimental *T. cruzi* infection are $CD4^+$ lymphocytes (A. Ben Younes-Chennoufi et al., 1988. Cellular immunity to *Trypanosoma cruzi* is mediated by helper T cells $CD4^+$. *Trans. R. Soc. Trop. Med. Hyg., 82:* 84-89).

Yet, it is obvious that further studies are necessary, mainly in respect to two points, namely which soluble mediators are actually involved in triggering effector circuits leading to myocytolysis, and whether or not regulatory T cells bear a preferential T cell receptor gene rearrangement.