leaving a population of immature resistant cells which can be replenished from a pool of dormant tumour cells. Thus resistance in myeloma need not be acquired by changes in the phenotype of myeloma cells but may be endogenous, due to the differential drug sensitivity of subpopulations of cells within the tumour. It must be stressed, therefore, that effective drug treatment must kill the more primitive cell types such as the lymphoplasmacytoid cell.

Because myeloma exhibits a degree of differentiation in man, studies to find the stem cell of the disease are most important if future treatments are to produce longer disease-free intervals. Furthermore it will be necessary to assess whether potential precursor cells (lymphoplasmacytoid) synthesise and secrete immunoglobulin so that the disease can be effectively monitored.

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PARTICIPATION OF DENDRITIC CELLS IN VASCULAR LESIONS OF CHRONIC REJECTION OF HUMAN ALLOGRAFTS

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Summary Immunohistochemical techniques were used to investigate the pathogenesis of obliterative arteriopathy, a major obstacle to long-term solid organ allograft survival. T-lymphocytes, macrophages, and proliferating smooth muscle cells made up most of the thickened intima. More importantly, S100-protein-positive dendritic cells were also present in the intima, especially during active inflammation and smooth muscle cell proliferation. These are phenotypic characteristics of tissue "dendritic" cells, pivotal accessory cells in T-dependent immune reactions. Their localisation in the arterial wall signals the presence of an ongoing immunological reaction directed at native constituents of the artery or at exogenous antigens which permeate the damaged vessel wall.

Introduction

OBLITERATIVE arteriopathy (OBA), the commonest untreatable long-term complication of all solid organ allografts,[1-6] often results in graft failure. Histopathologically, the arteries affected by OBA are characterised by a much thickened intima that contains a proliferation of spindle, various inflammatory, and foamy cells.[1,4,6] OBA is thought to be due to an immunological reaction (allogeneic) to donor antigens present on or in the arteries,[2] because of the presence of circulating anti-graft antibodies,[7,8] vascular deposition of immunoglobulin and complement,[2,5] and arterial inflammation observed microscopically, and because donor-specific antibodies have been eluted from affected grafts.[8] The resultant vascular lesion is probably a consequence of a response to injury, in the way that atherosclerosis (AS) in the general population is said to be.[9] To improve understanding of the pathogenesis of OBA we have investigated, by the use of immunohistological methods, the lineage of the cells that participate in OBA lesions.

Materials and Methods

All recent heart (n = 7), kidney (n = 9), and liver (n = 7) allografts that failed because of chronic rejection (clinicopathological evaluation) and that provided sufficient tissue for immunohistological studies were reviewed.

4 μm sections were cut from formalin-fixed and paraffin-embedded blocks stained with haematoxylin and eosin, Masson's trichrome, and Verhoff/Van Gieson for elastic tissue. Paraffin-embedded sections were also stained with various antibodies (table I), by the avidin-biotin-complex (ABC) method.[10] Tissue sections stained for actin and S100 protein were exposed to protease XXIV for 2 min before incubation with the primary antibody. Histological positive and negative (substitution of non-immune sera for primary antibody) controls with the identical treatment were run for each antibody. Frozen-tissue embedded in optimum cold temperature compound was subjected to immunofluoresence staining by a simple indirect technique with appropriate fluoresceinated secondary antibodies. For negative controls, the primary antibody was omitted.

Results (Table II)

Light Microscopic Features of OBA

Many histopathological features were common to the affected arteries of all of the organ allografts. Differences between the organs and a more detailed description of the findings will be reported elsewhere.

The vessels most severely affected by OBA were those of medium size range, often the first and second order branching vessels. Intimal expansion of affected vessels led to concentric narrowing of the lumen, the degree of narrowing varying from 40% to total occlusion. Smaller arteries and arterioles showed mural widening with less noticeable intimal change.

TABLE I—ANTIBODIES USED FOR PHENOTYPIC ANALYSIS OF THE CELLS INVOLVED IN OBA

Antibody source*	Method†	Dilution	Specificity
Lysozyme (DAKO)	IPEX	1/1600	Myeloid cells, histiocytic cells, secretory epithelial cells.[10]
Actin (Biogenex)	IPEX	Prediluted	Smooth muscle cells, pericytes and myoepithelial cells.[11,12]
S100 protein (DAKO)	IPEX and IF	1/450	Neural and glial cells, melanocytes, myoepithelial and duct cells of salivary glands, chondrocytes, Langerhans cells, "dendritic" cells and some macrophages.[10,13]
UCHL-1 (DAKO)	IPEX	1/40	Most thymocytes and activated T-cells; only a fraction of "resting" T-cells are positive.[14]
HLA-DR (Becton Dickinson)	IF	1/8	B-cells, activated T-cells, monocytes, macrophages, dendritic cells, and cells of inflamed tissues.
Leu-4 (CD3) (Becton Dickinson)	IF	1/20	Pan T-cell antigen and Purkinje cells of cerebellum.[10,15]

*DAKO, Santa Barbara, California; Biogenex, San Ramon, California; Becton Dickinson, Mountain View, California.
†IPEX = immunoperoxidase on paraffin-embedded tissue; IF = indirect immunofluorescence on frozen tissue.

TABLE II—SUMMARY OF PHENOTYPIC ANALYSIS OF CELLS INVOLVED IN OBA*

Characteristics of OBA lesion	Heart	Liver	Kidney
Intimal infiltration with T-cells (UCHL-1+)	++	±	+
Intimal infiltration of monocytes, macrophages (lysozyme +, macrophage morphology)	+	++++†	++
Intimal dendritic cells (S100 +, dendritic morphology)	++	±	++
Other intimal inflammatory cells‡	++	±	+
Smooth muscle cell proliferation (actin positive morphology)	++	±	+++
Intimal sclerosis§	+++	+	+++
Disruption of internal elastic lamina	++	±	++
Medial infiltration with T-cells	±	±	±
Medial infiltration of monocytes/macrophages	+	++	++
Periadventitial accumulation of macrophages and T-cells	+	++	++

*Relative number of cells compared with other organs for the same antibody. Not a comparison of different antibodies.
†Many of the macrophages in the thickened intima of the liver are "foam" cells.
‡Plasma cells, eosinophils, and neutrophils. These are particularly prominent in the cardiac grafts.
§Appears to depend on the "age" of the lesion since most of the arteries in the organs mentioned will eventually progress to sclerosis.

The intima contained varying degrees of mononuclear inflammation, foam cells, and apparent smooth muscle cell proliferation (fig 1). Plasmacytic, neutrophilic, and eosinophilic inflammation was less commonly present, except in the cardiac allografts. In kidney and heart grafts the internal elastic lamina was often disrupted; in the liver it was mostly intact.

The appearance of the media and periadventitial space was similar in all the organs. The media was infiltrated to various degrees by macrophages, lymphocytes, and foam cells. The inflammatory cells were located in areas of degenerating smooth muscle cells. Affected arteries had cuffs of periadventitial inflammatory cells. These periarterial cells seemed to invade the media from without, as if the medial smooth muscle cells were the target of immunological injury.

Finally, although we did not examine sequential biopsy specimens, the changes seemed to progress with time. Early lesions showed much inflammation, accompanied by smooth muscle cell proliferation. Thereafter, the inflammation gradually subsided and the intima became sclerotic.

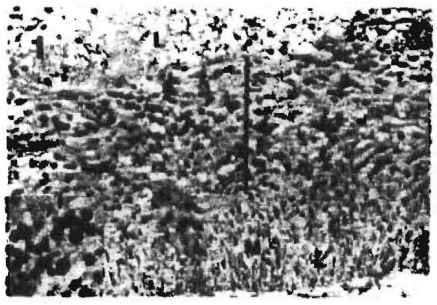

Fig 1—Characteristic OBA lesion showing intimal inflammation and thickening (H&E, approx 20 ×).

Note T-lymphocyte inflammation (inset, immunoperoxidase for UCHL-1 [T-cells]) and intimal thickening (arrowhead with line). L = arterial lumen, M = media.

Immunohistological Features

Various admixtures of macrophages (lysozyme-positive), T-lymphocytes (UCHL-1-positive, fig 1), proliferating smooth muscle cells (actin-positive), and S100-positive (S100+) cells were seen in the thickened intima of affected vessels. The variation, to some extent, was dependent on the age of the lesion and organ. The intimal S100+ cells were of two types. The first was round-to-oval with an oval, clefted, or angulated nucleus. These cells were uncommon; when present they were located immediately subjacent to the endothelium. The second type of S100+ cell was dendritic in shape (fig 2) and was usually found in contact with nearby T-lymphocytes and/or plasma cells and occasionally macrophages. The S100+ dendritic cells were located deeper in the intima, near the internal elastic lamina. Activated and proliferating smooth muscle cells were seen in two locations—immediately subjacent to hypertrophied endothelial cells, and deep in the intima, near the disrupted elastic lamina. Macrophages (lysozyme+, fig 3), T-lymphocytes, and the occasional S100+ dendritic cell were also seen in the media. The cuffs of inflammatory cells in the periadventitial space consisted predominantly of macrophages (lysozyme+). T-lymphocytes were less common. S100+ dendritic cells and/or terminal nerve twigs were even less so but easily recognisable.

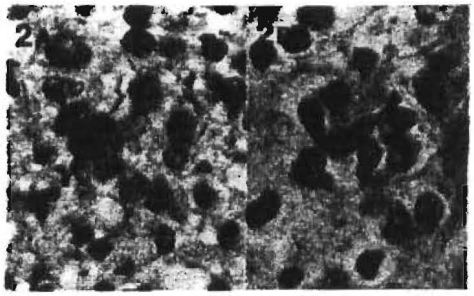

Fig 2—S100-protein-positive dendritic intimal cells (immunoperoxidase for S100 protein, approx 200 ×).

A—"spider" shaped processes; B—close association with lymphoid cells and macrophages.

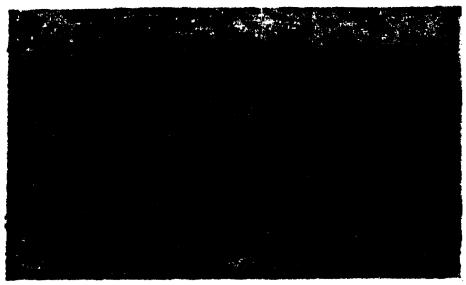

Fig 3—Lysozyme-positive cells (macrophages, immunoperoxidase for lysozyme, approx 80 ×) infiltrating the media from the adventitia.

L = Lumen; M = Media.

Serial 4 μm frozen sections consecutively stained for S100 protein and HLA-DR contained round (lymphocytic and histiocytic) HLA-DR-positive cells in the intima. Some HLA-DR + cells were spindle shaped. However, sections stained by immunofluorescence were not of sufficient quality to distinguish between smooth muscle cells and dendritic cells. Nevertheless, the elongated HLA-DR + cells were in the same general location as the S100 + ones.

Discussion

The presence of S100 +, and most likely, also of HLA-DR +, dendritic cells in arteries affected by OBA is strong evidence that these cells belong to the accessory, dendritic cell family.[17,18] Their localisation in the wall of damaged arteries of organ allografts is evidence of an ongoing immunological reaction involving T-lymphocytes in vessels affected by OBA.

Information on the physiology of dendritic cells is limited, since they have only recently been studied to any extent. It is clear, however, that they play a pivotal role in the immune response. Dendritic cells are derived from the bone marrow and constitute up to 0·5% of peripheral blood mononuclear cells.[19] They are extremely efficient accessory cells that normally express a high density of surface HLA-DR antigens and are potent stimulators of mixed lymphocyte reactions (MLR)—10–100 times more so than macrophages in these respects.[20-27] Dendritic cells may also express complement receptors, but are unable to "process" particulate antigens because of the lack of endophagocytic and lysosomal activity.[19,25] Therefore, dendritic cells may associate with typical macrophages, whose phagocytic and lysosomal activities compensate for these deficiencies.[25] The presence of dendritic cells in the thymus[28] and at sites of antigen processing and inflammation,[25,27] combined with in-vitro studies,[22,26] demonstrate their importance in T-cell-dependent immune responses. Once dendritic cells are "primed" with antigen, they interact with CD4 + T-helper cells, which are induced to undergo blastogenesis and clonally restricted proliferation. These activated helper cells are then able to interact with B lymphocytes and other cells necessary for the generation of the effector phase of the immune response.[22,26,27] Once an effector cascade develops, release of lymphokines and the local production of leukotrienes may induce smooth muscle cell[29] and/or fibroblastic proliferation and collagen deposition.

Indirect evidence suggests that the S100 + dendritic cells infiltrating the arteries are host (recipient) derived. First, no dendritic cells are detectable in the arteries of normal tissue[13] (and unpublished observation). Therfore, those that appear in the vessels, like the other inflammatory cells, probably originate from the bone marrow. Secondly, although dendritic cells may retain the capacity to divide, they have a short lifespan of 3–5 days.[30]

The role of dendritic cells in the OBA process is uncertain and therefore open to speculation. Traditionally, the endothelium is thought to be the target of immunological damage in primary humoral and "hyperacute" rejection. This assumption is probably correct. However, medial and proliferating intimal smooth muscle cells may also be the target of cellular and/or humoral reactions since they too express HLA-DR antigens when damaged.[31,32] The preferential involvement at vessel branch points may coincide with the location of smooth muscle cell containing intimal "cushions".[33] Alternatively, dendritic cells may play a more passive role. The artery affected by OBA may be extremely "leaky", permitting the passage of antigens into the vessel wall. The deep intima and media then become a site of intense antigenic stimulation, similar to mucosal or skin surfaces.

We noted a considerable number of S100 + dendritic cells in the interstitium of rejecting organs (data not presented). They were present when inflammatory destruction was taking place and became less frequent as the inflammation subsided and the organ assumed a "burnt out" appearance. Although these observations are limited, the role of both donor and recipient dendritic cells in the initiation and maintenance of allograft rejection should be a fruitful area of investigation.

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Preliminary Communication

INCREASE IN MYOCARDIAL G_i-PROTEINS IN HEART FAILURE

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Summary The contractile response and myocardial content of G_i-proteins were examined in cardiac preparations from explanted hearts of four different patients with end-stage heart failure. Three patients had idiopathic dilated cardiomyopathy and one patient had inflammatory heart disease. Preparations from patients with idiopathic dilated cardiomyopathy showed reduced contractile response to the cAMP-increasing agent isoprenaline and an increase in myocardial G_i-proteins, compared with preparations from non-failing hearts. Therefore it is conceivable that an increase in myocardial G_i-proteins is causally related to heart failure due to idiopathic dilated cardiomyopathy. In the preparation from the patient with inflammatory heart disease the contractile response to isoprenaline was not reduced and likewise content of G_i-proteins was not changed.

INTRODUCTION

DEFICIENT production of cAMP has been regarded as an important cause of contractile dysfunction in patients with end-stage heart failure. For instance, compared with controls, in severe heart failure adenylate cyclase activity is reduced,[1] and there is diminished contractile response to compounds that increase cAMP content via adrenoceptor-stimulation (β-adrenergic agents) or inhibition of cAMP degradation (phosphodiesterase inhibitors[2-4]). The reason for this effect might be an alteration of specific guanine nucleotide binding regulatory proteins (G-proteins).[4] In the heart the activity of adenylate cyclase is controlled by two G-proteins—G_s, which stimulates, and G_i, which inhibits, the enzyme.[5] We report here on the amount of myocardial G_i-proteins, as detected with pertussis toxin labelling, in heart failure due to idiopathic dilated cardiomyopathy.

PATIENTS AND METHODS

Three non-failing hearts were obtained from multiorgan donors whose hearts could not be used for surgical reasons or because of blood group incompatibility. The ventricles of these hearts looked normal. Four failing hearts were obtained from patients with end-stage heart failure undergoing orthotopic heart transplantation—three of these patients had idiopathic dilated cardiomyopathy, and one had myocarditis. The patient with myocarditis had a cardiac index of 1·6 l/min per m², did not improve with intravenous drug therapy, and therefore required urgent orthotopic heart transplantation. Informed consent was obtained from the families of all donors of non-failing hearts and from patients undergoing cardiac transplantation before explantation of the heart. Aortic and pulmonary valves were excised from non-failing hearts and used later for valve replacement. The patients were aged 27 to 56 years. The hearts were assayed for G_i-proteins. Membranes prepared from the hearts were incubated with ^{32}P-NAD in the presence of pertussis toxin and subjected to SDS-polyacrylamide electrophoresis and autoradiography as follows.

Tissue was rapidly frozen in liquid nitrogen and stored at −70°C. Membranes were prepared[6] from 1 g right ventricular tissue homogenised for 30 s with a 'Polytron' homogeniser (PT 10–35, Kinematica GmbH, Lucern, Switzerland) in 10 ml buffer containing 50 mmol/l "tris"-HCl (pH = 7·5), 5 mmol/l $MgCl_2$, 5 mmol/l edetic acid (EDTA), 1 mmol/l ethyleneglycol-bis-(β-aminoethyl ether) N,N'-tetraacetic acid (EGTA), and 50 kallikrein inhibitory units/ml aprotinin. The homogenate was centrifuged at 1000 *g* for 10 min at 4°C. The resultant supernatant was centrifuged at 40 000 *g* at 4°C, and the pellet was washed twice with the same buffer and stored at −70°C. ADP-ribosylation was done as previously described.[7] In brief, samples were diluted 10-fold with 20 mmol/l "tris"-HCl (pH = 8), 1 mmol/l EDTA, 1 mmol/l dithiothreitol (DTT), 3 mmol/l $MgCl_2$ and 10% sucrose, 0·1% Lubrol PX. 10 µl of diluted samples were added to a solution (80 µl) such that the final concentrations were 100 mmol/l "tris"-HCl (pH = 8), 10 mmol/l thymidine, 1 mmol/l EDTA, 1 mmol/l DTT, 1 mmol/l L-alpha-dimyristoyl phosphatidylcholine, and 2·5 µmol ^{32}P NAD (5000–10 000 cpm/pmol; NEN, Dreieich, West Germany). The reaction was started by the addition (10 µl) of 100 µg/ml of pertussis toxin (List Biological Laboratories, Campbell, California, USA). The reaction was terminated by addition of 100 µl Lämmli sample buffer (1% sodium dodecyl sulphate [SDS], 5% 2-mercaptoethanol, 10% glycerol, 62·5 mmol "tris"-HCl, 0·02% bromphenol blue, pH = 6·8) and heated at 95°C for 3 min. 25 µl of the solution was loaded on each lane of a 1 mm thick polyacrylamide slab gel (main gel, 12·5% acrylamide; packing gel, 4·5% acrylamide, 0·1 SDS) and subjected to electrophoresis according to Lämmli[8] in a conventional vertical slab gel electrophoresis chamber ('Mini-Protean II', Bio-Rad, München,

SHIRO OBUMA AND OTHERS: REFERENCES—*continued*

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