

## T cell subsets and expression of immunological activation markers in the arterial walls of patients with giant cell arteritis

RUNE ANDERSSON,<sup>1</sup> ROLAND JONSSON,<sup>2</sup> ANDREJ TARKOWSKI,<sup>3</sup>  
BENGT-ÅKE BENGTTSSON,<sup>4</sup> AND BO-ERIC MALMVALL<sup>5</sup>

From the <sup>1</sup>Department of Infectious Diseases, Östra Hospital, University of Göteborg, Göteborg, Sweden; the <sup>2</sup>Department of Oral Pathology, Faculty of Odontology, University of Göteborg, Göteborg, Sweden; the <sup>3</sup>Departments of Medical Microbiology and Rheumatology, University of Göteborg, Göteborg, Sweden; the <sup>4</sup>Department of Internal Medicine II, Sahlgrenska Hospital, University of Göteborg, Göteborg, Sweden; and the <sup>5</sup>Department of Infectious Diseases, Jönköping Hospital, Jönköping, Sweden

**SUMMARY** Immunohistochemical features of infiltrating mononuclear cells (MNC) and resident cells were studied in the temporal artery biopsy specimens of 13 patients with histological verified giant cell arteritis (GCA) and in six biopsy specimens from patients with GCA with negative histological findings. Eight temporal artery biopsy specimens from seven patients with unrelated diseases served as controls. In all patients with GCA proved by biopsy an infiltration of T lymphocytes in the arterial wall was observed, most being of the helper/inducer subset. No B lymphocytes, or very few, were seen. Lymphocytes in 10 out of the 13 positive biopsy specimens displayed staining for the class II major histocompatibility complex (MHC) antigen HLA-DR, whereas this was found in only two of eight controls. A minor number of the infiltrating T lymphocytes from seven out of 13 patients with GCA proved by biopsy stained for transferrin receptors, and in six out of the 13 cases they reacted with anti-interleukin 2 receptor antibody. In the arterial wall from all patients with histologically verified GCA we also found an increased number of macrophages, many of them expressing HLA-DR antigens and transferrin receptors. The immunohistochemical pattern of cell phenotypes found in the arterial wall of patients with GCA suggests that the infiltrating T cells are immunologically activated. This finding supports the hypothesis of a predominantly cellular immunological pathogenesis of giant cell arteritis.

**Key words:** immunohistochemistry, T lymphocytes, interleukin 2 receptor, HLA-DR, transferrin receptor, macrophages, B lymphocytes, natural killer cells, polymyalgia rheumatica.

Giant cell arteritis (GCA) is a vascular disease of unknown aetiology. Both humoral and cellular mechanisms have been implicated in the pathogenesis of GCA. The hypothesis of GCA as a humoral, immunologically mediated disease is supported by the finding of immunoglobulin and complement deposits in the arterial walls.<sup>1-4</sup> The demonstration of increased serum levels of IgG and complement and the detection of circulating immune complexes<sup>5-8</sup> also support this hypothesis. There is, however, some disagreement about the local

immunoglobulin and complement deposits<sup>9</sup> and the levels of serum immune complexes.<sup>10</sup>

In connection with the assumption of cell mediated immunity it should be noted that several authors have reported a decreased number of T lymphocytes of the cytotoxic/suppressor subset in blood from patients with GCA.<sup>11-13</sup> Elling and Elling found a connection between increased disease activity and the decreased numbers of cytotoxic/suppressor lymphocytes,<sup>12</sup> which is in contrast with observations made by Benlahrache *et al.*<sup>11</sup> No differences in lymphocyte antigenic responses between patients with GCA and normal controls have been found.<sup>14</sup>

Only limited and conflicting information is so far available about the phenotypes and activation status of lymphocytes in arterial lesions in GCA.

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Correspondence to Dr Rune Andersson, Department of Infectious Diseases, Östra Hospital, University of Göteborg, S-41685 Göteborg, Sweden.

Table 1 Clinical data and immunohistochemical findings in 27 temporal artery specimens from 13 patients with GCA and positive biopsies, six patients with GCA and negative biopsies and seven patients with unrelated diseases

| Patient No                                   | Age | Sex | Diagnosis                               | Corticoid treatment (days) | Relative occurrence* of cells reacting with: |               |                            |                                  |               |              | HLA-DR      |              | Transferrin receptor |     | Macro-phages (Leu M3) | NK cells* (anti-asiado GM1) |
|--|-----|-----|---|----------------------------|--|---------------|----------------------------|----------------------------------|---------------|--------------|-------------|--------------|----------------------|-----|-----------------------|-----------------------------|
|  |     |     |   |                            | pan-B (Leu 12)                               | pan-T (Leu 4) | T helper/ inducer (Leu 3a) | T suppressor/ cytotoxic (Leu 2a) | IL2* receptor | Lympho-cytes | Other cells | Lympho-cytes | Other cells          |     |                       |                             |
| <b>Patients with GCA and positive biopsy</b> |     |     |   |                            |  |               |                            |                                  |               |              |             |              |                      |     |                       |                             |
| 1  | 80  | F   | TP                                      | 0                          | 0  | +++           | +++                        | 0                                | 0             | ++           | +++         | +            | ++                   | +++ | +                     |                             |
| 2  | 78  | F   | TP                                      | 3                          | 0  | +++           | +++                        | 0                                | 0             | +            | +++         | 0            | 0                    | ++  | +                     |                             |
| 3  | 80  | F   | G                                       | 10                         | 0  | +++           | +++                        | ++                               | +             | ++           | +++         | +            | ++                   | +++ | 0                     |                             |
| 4  | 77  | F   | T                                       | 0                          | 0  | +++           | +++                        | ++                               | +             | ++           | +++         | +            | ++                   | +++ | +                     |                             |
| 5  | 80  | F   | T                                       | 0                          | +  | +++           | +++                        | +++                              | +             | +++          | +++         | +            | +++                  | +++ | +                     |                             |
| 6  | 90  | F   | PMR                                     | 5                          | 0  | +++           | +++                        | +++                              | +             | ++           | +++         | +            | ++                   | +++ | +                     |                             |
| 7  | 58  | F   | T                                       | 0                          | 0  | ++            | ++                         | 0                                | 0             | ++           | ++          | +            | ++                   | ++  | 0                     |                             |
| 8  | 71  | F   | TP                                      | 0                          | +  | +++           | +++                        | ++                               | +             | ++           | +++         | +            | ++                   | +++ | +                     | +                           |
| 9  | 78  | F   | TP                                      | 7                          | +  | +++           | +++                        | +                                | +             | ++           | +++         | +            | ++                   | +++ | +                     |                             |
| 10   | 63  | F   | T                                       | 0                          | 0  | ++            | ++                         | 0                                | 0             | 0            | 0           | 0            | 0                    | ++  | 0                     |                             |
| 11   | 66  | F   | TP                                      | 0                          | 0  | ++            | ++                         | 0                                | 0             | 0            | 0           | 0            | 0                    | ++  | +                     |                             |
| 12   | 75  | F   | G                                       | 0                          | +  | +++           | +++                        | ++                               | +             | ++           | +++         | +            | ++                   | +++ | +                     |                             |
| 13   | 71  | F   | PMR                                     | 0                          | 0  | +++           | +++                        | ++                               | 0             | 0            | +           | 0            | ++                   | ++  | 0                     |                             |
| <b>Patients with GCA and negative biopsy</b> |     |     |   |                            |  |               |                            |                                  |               |              |             |              |                      |     |                       |                             |
| 14   | 60  | F   | PMR                                     | 5                          | 0  | 0             | 0                          | 0                                | 0             | 0            | 0           | 0            | 0                    | +   | +                     |                             |
| 15   | 81  | F   | PMR                                     | 0                          | +  | +             | +                          | 0                                | 0             | +            | +           | 0            | +                    | +   | +                     |                             |
| 16   | 69  | F   | TP                                      | 0                          | 0  | 0             | 0                          | 0                                | 0             | 0            | 0           | 0            | 0                    | +   | 0                     |                             |
| 17   | 55  | F   | TP                                      | 0                          | 0  | +             | +                          | 0                                | 0             | 0            | 0           | 0            | 0                    | +   | 0                     |                             |
| 18   | 67  | F   | PMR (relapse)                           | 1                          | 0  | 0             | +                          | 0                                | 0             | 0            | 0           | 0            | 0                    | 0   | +                     |                             |
| 19   | 56  | F   | PMR                                     | 0                          | 0  | 0             | 0                          | 0                                | 0             | 0            | 0           | 0            | 0                    | 0   | +                     |                             |
| <b>Patients with unrelated diseases</b>      |     |     |   |                            |  |               |                            |                                  |               |              |             |              |                      |     |                       |                             |
| 20‡  | 76  | M   | Cancer of the gall bladder              | 0                          | 0  | 0             | 0                          | 0                                | 0             | 0            | +           | 0            | 0                    | +   | 0                     | 0                           |
| 21‡  |     |     |   | 0                          | 0  | 0             | +                          | 0                                | 0             | +            | +           | 0            | 0                    | 0   | +                     | +                           |
| 22   | 88  | F   | Pneumonia                               | 0                          | 0  | 0             | 0                          | 0                                | 0             | 0            | 0           | 0            | 0                    | +   | 0                     | 0                           |
| 23   | 71  | F   | Urinary tract infection                 | 0                          | 0  | 0             | 0                          | 0                                | 0             | 0            | 0           | 0            | 0                    | +   | 0                     | 0                           |
| 24   | 73  | F   | Myeloma                                 | 0                          | +  | +             | +                          | +                                | 0             | 0            | +           | 0            | +                    | +   | +                     | +                           |
| 25   | 73  | M   | Leg ulcers                              | 0                          | 0  | 0             | 0                          | 0                                | 0             | 0            | 0           | 0            | 0                    | +   | +                     | +                           |
| 26   | 78  | M   | Suspected pneumonia, pernicious anaemia | 0                          | +  | +             | +                          | 0                                | 0             | +            | +           | 0            | 0                    | +   | +                     | +                           |
| 27   | 50  | F   | Septicaemia, Staph aureus               | 0                          | 0  | 0             | +                          | 0                                | 0             | 0            | +           | 0            | 0                    | +   | +                     | +                           |

\*IL2=interleukin 2; NK cells=natural killer cells; T=temporal arteritis; TP=temporal arteritis+polymyalgia rheumatica; PMR=polymyalgia rheumatica; G=general symptoms only in GCA; +0=no staining; + to ++++=estimated relative occurrence; ‡specimens 20 and 21 were from the same patient.

The aim of this study was to characterise the phenotypes of infiltrating MNC in the temporal arteries of patients with GCA and to study the prevalence of immunological activation markers on these cells.

## Patients and methods

### PATIENTS

Twenty seven temporal artery specimens from 26 patients were studied. The biopsies were performed during the years 1982–6 at the department of otorhinolaryngology at Östra Hospital in Göteborg. The patients were treated at the departments of internal medicine and infectious diseases. Thirteen of the biopsy specimens showed histological signs of giant cell arteritis (i.e., positive biopsy) on examination by routine light microscopy. Six patients had giant cell arteritis according to clinical criteria<sup>15</sup> but a negative biopsy. As controls, we used eight biopsy specimens from seven patients who proved to have other, unrelated diseases. In none of the biopsy specimens from patients with GCA were signs of any significant atherosclerotic process found. Clinical features of all patients included in the study are summarised in Table 1.

The patients with GCA were divided into the following clinical groups, as previously described<sup>15</sup>: (a) localised temporal arteritis (T); (b) polymyalgia rheumatica (PMR); (c) temporal arteritis and polymyalgia rheumatica (TP); and (d) general symptoms (G) with no clinical symptoms from the temporal area or proximal muscles.

### METHODS

The biopsy specimens were transported to the laboratory in a buffered medium (Histocon, Göteborg, Sweden), were rapidly frozen with dichlorodifluoromethane spray, and stored at  $-70^{\circ}\text{C}$ .

The following monoclonal antibodies were used: anti-Leu 4 (CD3), anti-Leu 3a (CD4), anti-Leu 2a (CD8), anti-Leu 12 (CD19), anti-Leu M3 (CD14), and anti-transferrin receptor (Becton and Dickinson, Sunnyvale, CA, USA); anti-HLA-DR and anti-interleukin 2 receptor (CD25) (Dakopatts, Glostrup, Denmark); anti-asialo GM1 (Wako, Osaka, Japan). Anti-Leu 4 detects all T cells, anti-Leu 3a reacts with the helper/inducer T cell subset, and anti-Leu 2a reacts with the suppressor/cytotoxic T cell subset. Anti-Leu 12 reacts with all B lymphocytes, anti-Leu M3 with the macrophages, and anti-asialo GM1 with the natural killer (NK) cells. Serial sections from the arteries (6  $\mu\text{m}$  thick) were prepared in a cryostat. The sections were fixed in cold acetone for five minutes, washed in phosphate buffered saline (PBS), and endogenous peroxidase blocked by

treatment with 0.3%  $\text{H}_2\text{O}_2$  for 10 minutes. After additional washes in PBS the sections were incubated for 30 minutes in a humidified chamber at room temperature with 50  $\mu\text{l}$  portions of monoclonal antibodies diluted in PBS containing 4% bovine serum albumin (PBS-BSA). Biotin labelled anti-mouse immunoglobulin (Vector Laboratories, Burlingame, CA, USA) diluted in PBS-BSA was used as the secondary reagent. Binding of biotin labelled antibodies was detected after incubation with avidin-biotin-peroxidase complexes (Vector)<sup>16</sup> and by subsequent use of  $\text{H}_2\text{O}_2$  and a buffer containing 3-amino-9-ethylcarbazole. All sections were counterstained with Mayer's haematoxylin.

## Results

The immunohistochemical findings are presented in Table 1 and Figs 1 and 2. In all the patients with GCA and a positive artery biopsy on routine microscopy we found an abundant infiltration of MNC, most of them reactive with Leu 4 (pan-T) antibody. Most of these cells expressed the helper/inducer (Leu 3a) phenotype. A minor portion of the MNC expressed the suppressor/cytotoxic (Leu 2a) phenotype. The anti-Leu 3a antibody reacts not only with T lymphocytes but also with some non-lymphocytic cells.<sup>17,18</sup> It was possible, however, to estimate the number of lymphocytes stained with anti-Leu 3a by the cell morphology. No B lymphocytes, or only a few, were found, as ascertained by negative staining with anti-Leu 12.

The MNC in 11 out of the 13 positive biopsy specimens showed staining for HLA-DR antigen. The prevalence of stained MNC corresponded with the degree of inflammation as assessed by the amount of infiltrating cells. Both lymphocytes and some of the cells in close connection with the infiltrating lymphocytes were stained. The distribution of macrophages was similar to the expression of HLA-DR antigen, indicating that a large proportion of the non-lymphoid HLA-DR positive cells were probably macrophages. In five out of the eight control biopsy specimens expression of HLA-DR antigen was infrequently observed.

Staining for transferrin receptor was visible on some of the T cells in seven out of the 13 patients with positive biopsies but none of the eight controls. Transferrin receptor stain was also found diffusely around the fragmented internal elastic lamina. Some of the transferrin receptor positive cells had the morphological appearance of macrophages (Figs 1d and e), and in serial sections the similar cells were stained with anti-Leu M3. The prevalence of interleukin 2 receptors displaying lymphocytes was low in six out of 13 positive biopsy specimens. A low

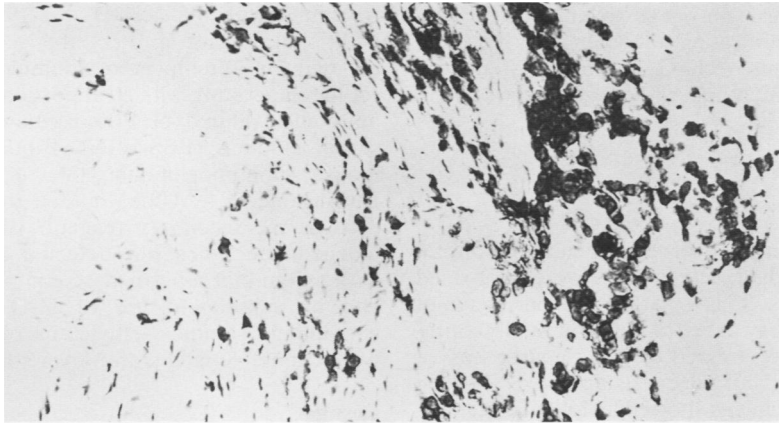


Fig. 1a

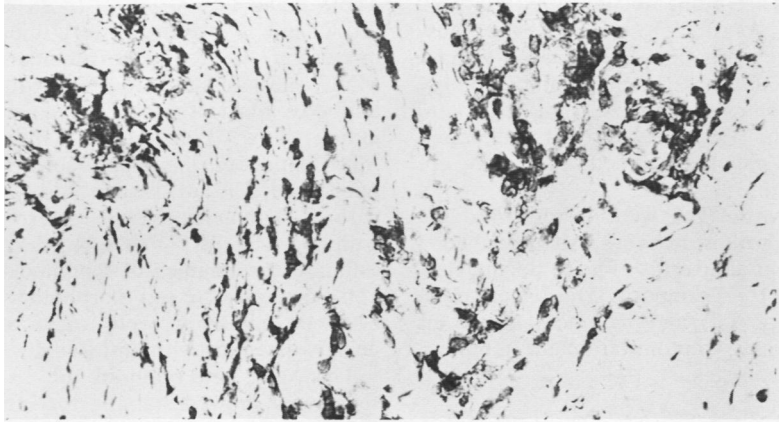


Fig. 1b

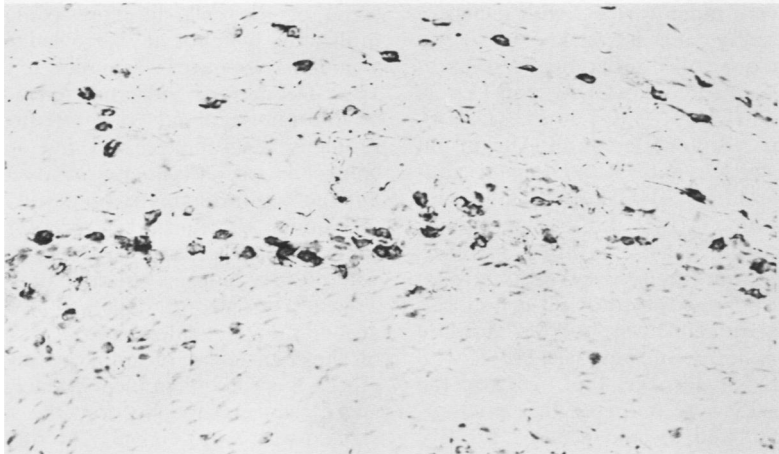


Fig. 1c

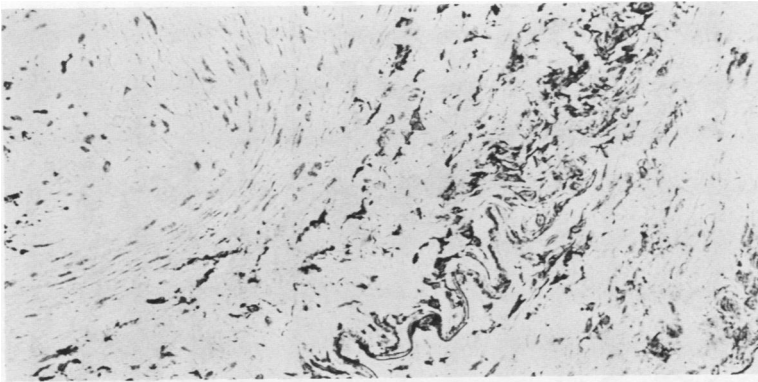


Fig. 1d

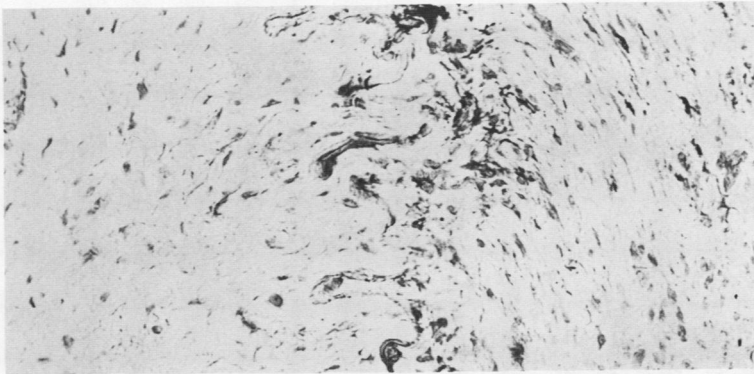


Fig. 1e



Fig. 1f

**Fig. 1** Immunoperoxidase staining of the temporal artery from an 80 year old woman with giant cell arteritis (patient No 3) using monoclonal antibodies against (a) Leu 4=all T lymphocytes; (b) Leu 3a=helper/inducer T lymphocytes; (c) Leu 2a=suppressor/cytotoxic T lymphocytes; (d) Leu M3=macrophages; (e) transferrin receptor; (f) HLA-DR.

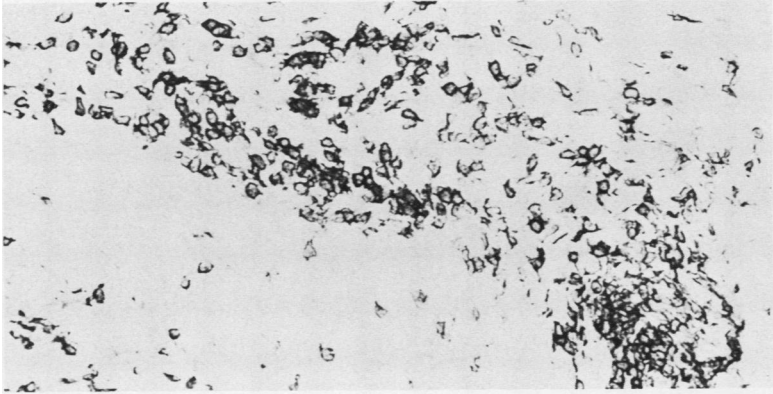


Fig. 2a

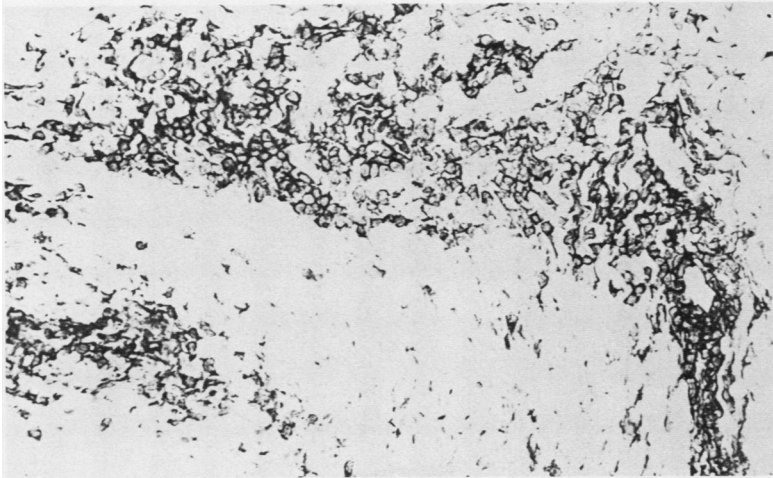


Fig. 2b

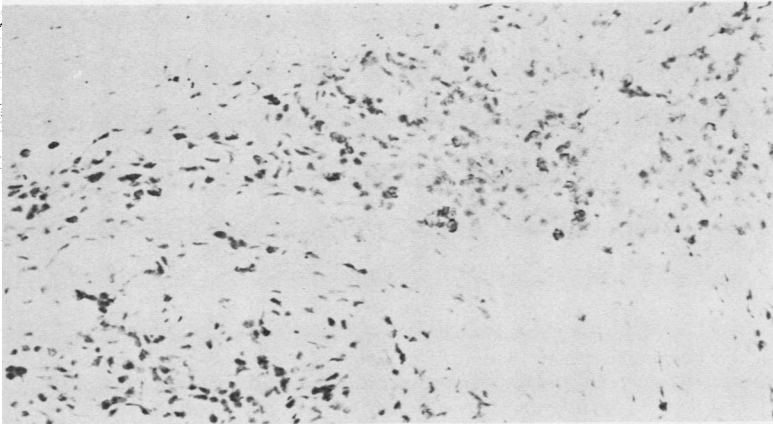


Fig. 2c

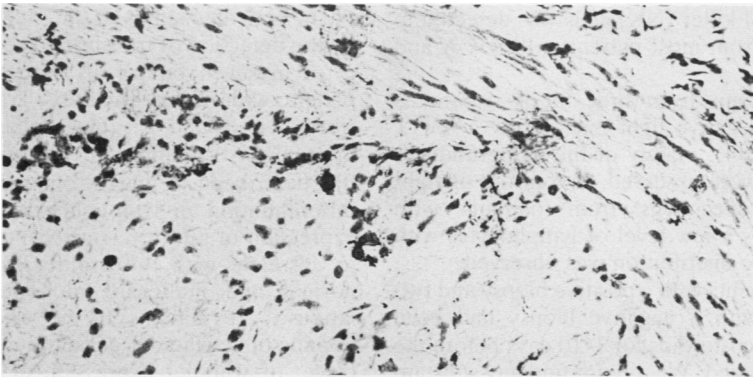


Fig. 2d

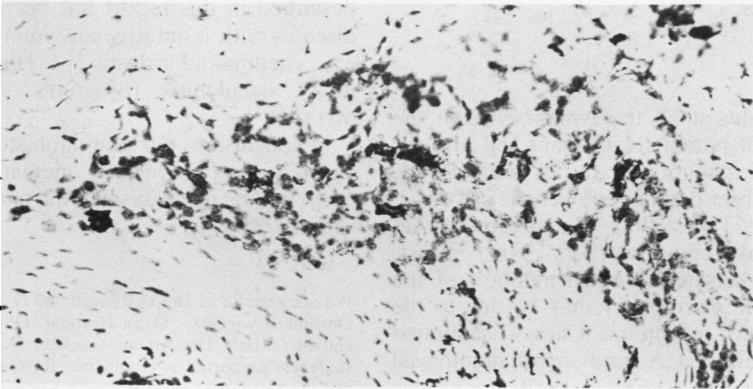


Fig. 2e

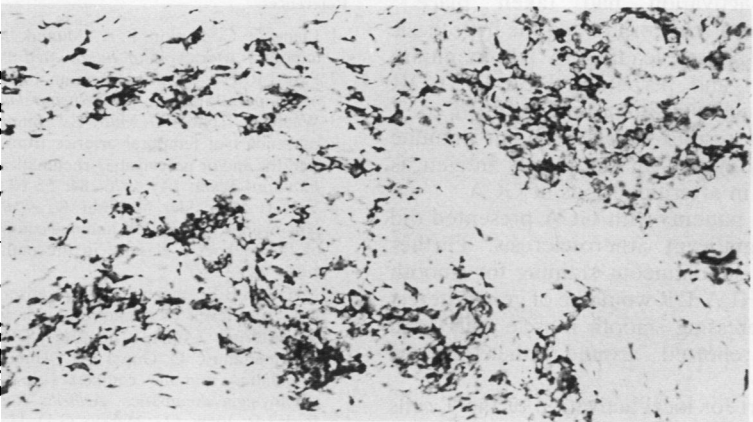


Fig. 2f

**Fig. 2** Immunoperoxidase staining of the temporal artery from a 75 year old woman with giant cell arteritis (patient No 12) using monoclonal antibodies against (a) Leu 4=all T lymphocytes; (b) Leu 3a=helper/inducer T lymphocytes; (c) Leu 2a=suppressor/cytotoxic T lymphocytes; (d) Leu M3=macrophages; (e) transferrin receptor; (f) HLA-DR.

number of natural killer (NK) cells was detected in the arterial wall from most patients with GCA and most controls.

In biopsy specimens from three out of six patients with GCA and negative light microscopy a few T lymphocytes (Leu 4), mainly of the helper/inducer (Leu 3a) subset, were observed. In four out of eight control biopsy specimens from patients with unrelated diseases a low level of lymphocytes with similar phenotypic distribution was observed.

Four of the patients with a positive biopsy and two of the patients with a negative biopsy had been treated with corticosteroids for 1–10 days before the biopsy was performed. We did not find any substantial differences for the phenotype markers of the lymphocytes in arterial specimens from treated and untreated patients.

### Discussion

We found that almost all the lymphocytes in the arteritic lesions of patients with giant cell arteritis expressed T cell phenotype. In all patients the helper/inducer subset dominated over the cytotoxic/suppressor subset. This finding is in agreement with the work of Banks and coworkers.<sup>19</sup> In contrast, Chess and coworkers found equal numbers of the two subsets.<sup>20</sup> The discrepancy may be due to the difference in patient selection as Chess *et al* studied only patients with GCA and ophthalmological symptoms.

A large number of the MNC in the arteritic lesions expressed HLA-DR antigens, indicating that immunological activation had taken place.<sup>21</sup> Klareskog and coworkers formulated the hypothesis that immune responses leading to autoimmunity may be initiated and perpetuated by HLA-DR positive cells which locally present antigen to T cells.<sup>22</sup> Thus our results suggest that an immune reaction, possibly against an autologous antigen, is occurring locally in arteritic lesions of GCA.

In none of the patients with GCA presented did we find any significant atherosclerosis. Further studies including simultaneous staining for smooth muscle cells and HLA-DR would be of great interest as HLA-DR expressing smooth muscle cells have recently been reported around atherosclerotic plaques.<sup>23–25</sup>

Further support for local activation of the T cells was the finding of interleukin 2 receptors on the lymphocytes in six out of 13 biopsy specimens with signs of arteritis. As interleukin 2 receptor expression is a prerequisite of subsequent IL2 binding and activation of T cells<sup>26</sup> our findings further emphasize that lymphocytes found in arteritic lesions are stimulated.

The activated status of the T cells was also shown by the detection of transferrin receptors on lymphocytes in seven out of 13 biopsy specimens from patients with giant cell arteritis. Transferrin receptors were also found on macrophages close to the internal elastic lamina. The transferrin receptor was first described as a marker of an early stage of T cell differentiation in lymphoblastic leukaemia.<sup>27</sup> The expression of a transferrin receptor has been found to correlate with the proliferation status in both normal and malignant mononuclear cell populations.<sup>28</sup> It remains to be established whether homing of activated T cells into arteritic areas takes place, or whether expression of IL2R, transferrin receptor, and HLA-DR is induced *in situ*.

An immunohistochemical pattern similar to that described in this report has been found in several diseases with a putative autoimmune pathogenesis, e.g., rheumatoid arthritis,<sup>17–29</sup> Hashimoto's thyroiditis,<sup>30</sup> sialadenitis (Sjögren's syndrome),<sup>18</sup> and myositis.<sup>31</sup>

In conclusion, our immunohistochemical findings strongly support a cell mediated, possibly self perpetuating mechanism in the pathogenesis of giant cell arteritis.

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