T lymphocytes in patients with primary vasculitis: expansion of CD8+ T cells with the propensity to activate polymorphonuclear neutrophils

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Introduction
The aetiology and pathogenesis of primary vasculitides such as WG or microscopic polyangiitis (MPA) are still elusive. Although, autoantibodies to neutrophil-derived antigens—collectively referred to as ANCA—are found in the majority of patients, the causal relationship between these autoantibodies and the initiation or progression of the disease is still a matter of controversy [1–6].

From in vitro data it was deduced that antibodies to PR3 stimulate neutrophils (polymorphonuclear neutrophils; PMN) [7–11; reviewed in 3, 6]. Whether that occurs in vivo is questionable, because ANCA are of low affinity, and even in patients with antibody high titres, the PMN are negative for surface-bound antibodies [2]. ANCA are not detected on PMN that have infiltrated the tissue—e.g. in the kidney—despite the fact that those PMN express PR3 [12]. Moreover, ANCA are not deposited at inflamed sites, hence WG and MPA are described as pauci-immune. There is no doubt, however, that PMN are activated in acute disease: transfer of the ‘target’ antigens for ANCA, particularly of PR3 and of elastase, to the cell surface has been observed [13–15], as has up-regulation of activation-associated PMN functions, including up-regulation of MHC class II, thus generating the same PMN phenotype as in patients with active ANCA-associated vasculitis. A similar PMN phenotype could be generated by cultivation with supernatants of activated T cells or by IFN-γ alone, but not by antibodies to proteinase 3.

Conclusions. In active primary vasculitis, a small population of CD8+ T cells, identified by the expression of CD11b, expands, producing IFN-γ. These T cells could activate PMN, thus generating a long-living and potentially destructive PMN phenotype.

Key words: PMN, ANCA, Vasculitis, T cells, CD11b, CD28, CD8, WG, Microscopic polyangiitis.

Objectives. To gain insight into the immune pathogenesis of primary ANCA-associated vasculitides, the prevalence of circulating T lymphocytes expressing CD11b as a marker for activation was analysed in patients with WG or MPA.

Methods. Receptor expression and IFN-γ synthesis were measured in T cells of patients with active disease by cytofluorometry and compared with expression in patients in remission and in healthy donors.

Results. During active disease, a small but conspicuous population of CD8+CD28+CD11b+ was found which produced IFN-γ. In healthy donors and in patients in remission or undergoing immunosuppressive therapy, CD11b was exclusively associated with CD8+CD28− cells, the latter being more frequent in patients with long-lasting or severe disease. In vitro experiments confirmed that CD11b is up-regulated when T cells are activated. After multiple rounds of restimulation, the CD11b expression persists whereas CD28 expression is lost, compatible with the notion that CD8+CD28−CD11b+ represents a transient phenotype in the course of T-cell activation. The IFN-γ-producing T cells activated polymorphonuclear neutrophils (PMN) to express MHC class II, thus generating the same PMN phenotype as in patients with active ANCA-associated vasculitis. A similar PMN phenotype could be generated by cultivation with supernatants of activated T cells or by IFN-γ alone, but not by antibodies to proteinase 3.

Conclusions. During acute viral infections, a small number of PMN differentiated to cells with dendritic-like characteristics: expression of MHC class II antigens and of the co-stimulatory receptors CD80 and CD86 is potent activators of numerous PMN functions, including up-regulation of MHC class II antigens, of the co-stimulatory antigens CD80 and CD86, of the Fc receptor CD64 and of integrins [21–23; reviewed in 24].

Participation of T lymphocytes in the pathogenesis of WG or MPA has long been postulated. Evidence for T-cell activation is derived from numerous studies analysing the surface receptor profile (reviewed in 4, 6 and [25–28]) or from therapy studies directed predominantly against T lymphocytes [29]. Moreover, we have provided evidence for replicative senescence of T-cell clones [30], which verifies T-cell activation as opposed to alterations within the T-cell compartment due to immunosuppressive therapy. Despite much effort, the specificity of the activated T cells, the activating events and the role of T cells in the pathogenesis of primary vasculitis are still elusive, although numerous attractive hypotheses have been forwarded [27, 28, 31, 32].

In the present study, the prevalence of circulating T lymphocytes expressing CD11b as a marker for activation was analysed in patients with active WG or MPA, and was compared with patients with inactive disease, or to healthy donors, respectively. CD11b, the β2 integrin Mac-1, also known as complement receptor 3 (CR3), is expressed on all leucocytes, including T cells. CD11b is up-regulated in the course of T-cell activation in both, CD4+ and CD8+ cells, and most probably participates in migration and extravasation of the cells [33]. From studies with virus-infected mice, it was concluded that CD11b might be the best single marker available for discriminating between naive and memory CD8+ cells [34], or effector and memory cells, respectively [35]. A study with patients suffering from acute viral infections supported this conclusion: during acute
virus infection, a population of CD8+CD28+ lymphocytes expressing CD11b develops with functional characteristics of memory/effector cells [36]. Moreover, our own studies of patients with bacterial infections revealed up-regulation of CD11b not only on CD8+ cells, but also on CD4+ cells.

In the current study, we found a small population of CD8+CD28+CD11b+ cells which declined upon immunosuppressive therapy in patients with active disease. The CD8+ cell produced IFNγ, and we propose that these T cells activate PMN, thus generating the PMN phenotype prevailing in active disease.

Patients and methods

Patient characteristics

The study was approved by the ethic committees of the University of Heidelberg and of the University of Düsseldorf. Between 1999 and 2006, after informed consent was obtained, 90 patients were recruited by the renal unit of the University of Heidelberg University Hospital and the Department of Rheumatology/Immunology of the University of Düsseldorf. Ten patients had active disease, with a BVAS (Birmingham vasculitis activity score) > 5 [37]. Of these patients, four had untreated, newly diagnosed WG, one had a relapse after remission for 2 yrs, and five had untreated, newly diagnosed MPA. Eighty patients in remission (BVAS < 1) (47 patients with WG and 33 with MPA) were also included. WG and MPA were classified according to the definition of the Chapel Hill conference [38] and to the ACR criteria for the current study. Patients were classified by the number of organs involved, history of more than one relapse. Furthermore, patients were divided into two groups: those with long-standing disease (> 5 yrs) and those with a disease duration of ≤ 5 yrs.

‘Severe disease’ was defined as follows: systemic disease including at least one major organ (e.g. kidney, lung, central nervous system), and history of more than one relapse. Furthermore, the cumulative cyclophosphamide dose was calculated for each patient. Patients were classified by the number of organs involved, as described by Reinhold-Keller et al. [40] and de Groot et al. [41]. For comparison, blood was drawn from healthy donors, matched with regard to age, after having obtained informed consent and observing the institutional guidelines.

Cytofluorometry

The expression of CD8, CD28 and CD11b was measured in whole blood by FACScan using standard procedures. Cells were triple-stained using phycoerythrin (PE) or APC-labeled antibodies to CD8 or CD4 (Becton Dickinson, Heidelberg, Germany), and FITC-labelled antibodies to CD28 (Serotec Düsseldorf, Germany; YTH 913.12) or CD11b (Biozol; Eching, Germany, ICRF44). A PE-labelled anti-CD11b was also used (BD Biosciences, Heidelberg). PMN were double-stained with the specific marker CD66b FITC (clone 80 H3) and with CD14 PE (clone UCHM1). CD64 PE (clone 10.1) or MHC Class II PE (clone WR18) (all these antibodies were purchased from Serotec). The antibody to PR3 (‘Pelcluster ANCA’) produced by Sanquin Amsterdam, was obtained from HISS Diagnostics Freiburg, Germany. The final concentration of antibodies varied between 1 and 10 μg/test. The isotype controls IgG1, IgG2a and IgG2b were used in the same final concentration. To determine the CD4/CD8 ratio, a mixture of anti-CD4 FITC- anti-CD8-PE was used with IgG FITC/IgG PE as control (antibodies obtained from Beckman Coulter, Marseille, France).

Production of IFNγ. Accumulation of IFNγ was measured intracellularly by cytofluorometry. The cells were treated with brefeldin A (10 μg/ml; Sigma, Munich, Germany) for 4–12 h, then incubated with 100 μl Fix and Perm solution (Becton Dickinson) and FITC-labelled antibody to IFNγ. Two different antibody clones were used: clone 25723.11 (BD Bioscience) and clone D9D10 (Serotec) in a final concentration of 10 μg/ml.

Analysis of the data

For technical reasons not all parameters were measured in all patients or healthy donors. The number of individuals that compared with regard to one particular parameter is given in the figure or the figure legend, respectively. The results of the FACScan data are expressed as percent positive cells in the respective gate in relation to CD8+ cells. Differences between groups were calculated by one-way analysis of variance (ANOVA) and Bonferroni test at a significance level of P < 0.05. The chi-square test was used to analyse the coincidence of low CD4/CD8 ratio and the expression of CD11b or CD28. The threshold for low CD4/CD8 ratio was set as < 1.5; the threshold for the other parameters was set using the respective mean values ± 1 S.D. obtained for healthy donors.

Isolation of T cells and PMN and in vitro activation

PMN. Whole blood was centrifuged on Polymorphprep® (Nycomed, Oslo, Norway) according to the supplier’s protocol. From the PMN layer, cells were further purified by adsorption to anti-Cd15 magnetic beads (AutoMACS) (Miltenyi Biotech, Bergisch Gladbach, Germany).

T cells. From the mononuclear cell layer, CD8+ were isolated by adsorption to anti-Cd8 magnetic beads.

Co-cultivation experiments: T-cell line. To generate a T-cell line expressing CD11b, the CD8+ cells were stimulated with phytohaemagglutinin (PHA) (1 μg/ml) and placed on irradiated autologous mononuclear cells as feeder cells (3 x 10⁶ CD8+ per 3 x 10⁶ feeder cells). After 24 h, IL-2 was added (2.5 ng/ml). After 16 days in culture, the T cells were harvested and stimulated again with PHA. After the second round of cultivation, 72% of the cells were positive for CD11b, after the 4th round 95% were positive. Of these, 83% were negative for CD28. For the co-culture experiments, equal numbers of T cells and of PMN (2 x 10⁶ in a total volume of 1 ml) were incubated for 24–48 h.

Isolated T cells. CD8+ cells derived from healthy donors were suspended in RPMI supplemented with fetal calf serum (10%), penicillin/streptomycin (1%), l-glutamine (1%), Hepes (1%) and IL2 (2.5 ng/ml) and were placed into multi-well culture dishes (24 wells) coated with anti-CD3 (clone UCH1-1, Immunotec, Marseille, France 100 ng/well) in a concentration of 10⁶ per well. An equal number of autologous PMN was added. After 48 h in culture, MHC class II expression on PMN was measured by cytofluorometry. For comparison, PMN were cultivated without T cells, or with T cells without stimulation.

Production of T-cell supernatants. CD8+ T cells derived from healthy donors were activated with PMA (20 ng/ml) and ionomycin [1 μg/ml for different time intervals (1, 4, 12, 24 and 48 h)]. Supernatants were harvested, IFNγ was measured by a commercially available ELISA (R&D Systems, Minneapolis, MN, USA), and 200 μl of the supernatant was added to PMN 2 x 10⁶ suspended in 800 μl AIM-V (Gibco, Eggenstein, Germany). MHC class II expression on the PMN was measured after 1, 24 and 48 h by cytofluorometry using an antibody to CD66b to identify the PMN.

Stimulation of PMN with anti-PR3. 1–5 μg of anti-PR3, and for comparison, mouse IgG, were added to isolated PMN or to whole blood. After 24 and 48 h, MHC class II expression was measured by cytofluorometry. Death of PMN was determined by propidium iodide staining.
Results

Analysis of PMN and of T cells in patients with active disease

Peripheral blood cells of patients with active WG ($n = 5$) or active MPA ($n = 5$) were analysed by cytofluorometry. On PMN, the following activation-associated receptors were up-regulated: CD66b; CD64 and MHC class II, the latter particularly on PMN of patients with WG. Moreover, surface expression of PR3 was detected in all patients, including the patients with MPA. Expression of MPO was seen in one of the MPA patients. After onset of the immunosuppressive therapy, the receptor expression declined within days (examples are shown in Fig. 1A; data of all parameters and patients are summarized in Fig. 1B).

Among the receptors tested on T lymphocytes, marked differences were seen for CD11b expression: on T cells of healthy donors CD11b expression was mainly associated with CD8+CD28− cells. In patients with active disease, a population of CD8+CD28+CD11b+ cells appeared, up to 18% of the CD8+ cells [mean $8.9 \pm 4.7\%$ vs $1.2 \pm 2.0\%$ in healthy donors ($n = 20$); $P < 0.001$]. In remission, the population of CD8+CD28+CD11b+ cells disappeared (an example is shown in Fig. 2A). On CD4+ cells, expression of CD11b was well below 1%.

The CD8+CD11b+ cells produced IFNγ ex vivo: when kept for 4h at 37°C in the presence of brefeldin A, IFNγ could be visualized intracellularly, predominantly in the CD11b+ cells (one of five patients is shown in Fig. 2B). Within days after onset of therapy with immunosuppressants, the IFNγ-producing cells were no longer detectable.

Analysis of CD8 T cells of patients in remission: loss of CD28 and expression of CD11b

As described above, CD8+CD28+CD11b+ cells were not detectable in patients in remission and in those patients CD11b was expressed exclusively on the CD28− cells (one of five patients is shown in Fig. 2B). Within days after onset of therapy with immunosuppressants, the IFNγ-producing cells were no longer detectable.
With regard to CD11b expression, there was no difference between patients with WG and patients with MPA.

Determination of CD4:CD8 ratio in the patients

The determination of the ratio of CD4+ to CD8+ cells is widely used to monitor alterations within the T-cell compartment.

As illustrated by histogram plotting, in the majority of patients in remission (58 of 80) the CD4:CD8 ratio was well below 1.5 (normal range 1.5–2.5) (Fig. 3A). A median value of 1.0 was determined for the patients and 2.05 for healthy donors (n = 50). The mean values (1.12 ± 0.56 for the patients and 1.81 ± 0.44 for the healthy donors) were significantly different as calculated by ANOVA and the Bonferroni test (significance level 10⁻⁵).
Notably, a low CD4:CD8 ratio correlated with a high percentage of CD8+CD28− cells (Fig. 3B), while there was no correlation regarding CD11b expression (Fig. 3C).

**In vitro experiments linking IFNγ-producing T cells and PMN**

So far, our data indicated that in patients with active WG CD8+CD28+CD11b+ cells expand, which *ex vivo* produced IFNγ without further activation. Because IFNγ is among the few cytokines able to induce the MHC class II expression on PMN, we attempted to test directly the interaction of CD8+CD28+CD11b+ cells with PMN *in vitro*. Since induction of MHC class II antigens requires 24–48 h autologous cells, these experiments could not be performed with CD8+CD28+CD11b+ cells from the patients, because during active disease, PMN are already activated. Therefore, we generated CD8+ expressing CD11b+ of healthy donors on up to 90% of the cells by *in vitro* activation. These cells also produced IFNγ (Fig. 4A–D, upper panel). When these cells were co-cultivated with autologous PMN, an up-regulation of MHC class II antigens on the PMN was observed. By 24 h, 12.7 ± 8.0% of PMN had acquired MHC class II; by 48 h it was 24.9 ± 7.5%. Expression of MHC class II on freshly isolated PMN was < 1% (Fig. 4E–H). In the absence of the T cells, the PMN did not acquire MHC class II, and the majority of PMN became apoptotic. In the presence of T cells, however, up to 80% of PMN survived (data not shown).

In another set of experiments, freshly isolated CD8+ cells were used in place of the T-cell line. When these cells were co-cultivated with PMN, the MHC class II induction was marginal. When, however, the T cells were placed on immobilized anti-CD3, and the PMN were added, MHC class II expression on the PMN was induced. On average, by 48 h, 10.5 ± 7.5% (mean ± s.d. of five independent experiments) of PMN acquired MHC class II. The induction of MHC class II on PMN paralleled the up-regulation of CD11b on the CD8+CD28+ cells (data summarized in Table 1).

In a further set of experiments, supernatants of PMA/ionomycin-activated CD8+T cells were used. With supernatants of cells having been activated for 24–48 h, MHC class II expression could be up-regulated. At these time points, IFNγ was maximally accumulated in the cell supernatant (depending on the individual donors, the IFNγ concentration amounted to 600–800 units/10⁶ cells after 24–48 h). Supernatants harvested after 1 h, which did not yet contain IFNγ, had no effect on MHC class II expression, ruling out direct effects of PMA/ionomycin on PMN. The up-regulation of MHC class II antigens on PMN could be inhibited by antibodies to the IFNγ receptor (data summarized in Fig. 5).

Since autoantibodies to PR3 are thought to play a role in PMN activation ([7, 9, 10, 45]; reviewed in [3, 6]), we assessed the effect of PR3 antibodies on the expression of MHC class II by PMN. Neither short-term nor long-term cultivating of PMN with anti-PR3 resulted in an up-regulation of MHC class II (Fig. 5).

**Discussion**

A hallmark of WG or MPA is the activation of PMN. Activated PMN are found in the peripheral blood, but also as infiltrates in affected tissues [12, 16–20]. Although PMN are mainly recognized for their role in host defence, there is strong evidence that they also participate in chronic inflammatory disease as major effectors of tissue destruction [46–49]. Activation of PMN is primarily attributed to bacterial products or pro-inflammatory cytokines (e.g. IL8). Less well-acknowledged is the fact that IFNγ, a typical T-cell-derived cytokine, is a potent activator of PMN. IFNγ induces a rather unique alteration of PMN; namely, the trans-differentiation of PMN to cells with characteristics of dendritic...
cells, including prolongation of the life span, acquisition of CD64, CD83, MHC class II and the co-stimulatory molecules CD80 and CD86, as well as the ability to function as accessory cells for T-cell activation ([20–23], reviewed in [24] and [50]).

We now propose that it is indeed the T-cell response that leads to the generation of IFN-γ to the activation of PMN in WG or MPA. Our proposition is based on the following facts: (i) during acute disease PMN are activated. Aside from the usual activation-associated receptors, MHC class II antigens and CD64 are up-regulated, both known to be induced by IFN-γ, but not by other inflammatory cytokines such as IL-8, or by complement activation products (for review see [50]) or by ANCA. (ii) There is unquestionable evidence that IFN-γ is generated during active disease and that it is critically involved in the pathogenesis, particularly of WG [51–54]; (iii) T cells are activated in the course of the primary vasculitides, and T-cell activation progresses over an extended period of time. Evidence includes the replicative senescence within the T-cell compartment [30], the reduced expression of CD28 [30, 42, 43, 51, 55, 56], the acquisition of CD57 [42] and the shift of the CD4:CD8 cell ratio (Fig. 3A).

How and why the T cells are activated has not yet been determined, nor has it been possible to unequivocally establish antigen specificity ([57–60]; reviewed in [28]). According to data in the literature, in WG or MPA both, CD4 and CD8, T cells are activated, and CD4 cells have been identified as a source of IFN-γ [51–54].

We now provide evidence for the activation of CD8+ cells during active disease. As a marker for T-cell activation, we determined CD11b expression, because studies with virus-infected mice have indicated that CD11b expression is not only a reliable

![Figure 4](http://example.com/figure4.png)

**FIG. 4.** Generation of CD8+CD11b+ cells in vitro and co-culture with PMN. Upper panel: peripheral CD8+ isolated from a healthy donor (A) were stimulated repeatedly with PHA. Expression of CD11b was determined after the second (B) and the fourth round (C) of re-stimulation. The majority of these CD8+CD11b+ cells synthesized IFN-γ (D). Lower panel: autologous PMN were added to CD8+ T cells derived from a healthy donor and activated by immobilized anti-CD3. After 48 h, expression of MHC class II on the PMN was measured. In the forward-side scatter image (E), the two cell populations can be seen. The gate was set around the PMN population (R1), and class II expression was measured (F) showing the isotype control. For comparison, PMN cultivated in the absence of T cells are shown (G), as are the PMN before culture (H). PMN acquire MHC class II only in the presence of T cells.

**TABLE 1.** Induction of MHC class II expression on PMN of healthy donors by CD8+ T cells

<table>
<thead>
<tr>
<th>Co-cultivation of isolated PMN with</th>
<th>MHC class II expression (percentage) of CD66b+ PMN after 24 h</th>
<th>MHC class II expression (percentage) of CD66b+ PMN after 48 h</th>
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<tr>
<td>Peripheral CD8+ cells</td>
<td>CD28+CD11b−CD11b+: 25.5–51.0, CD28+CD11b+: 0.12–1.2</td>
<td>2.5–5.5a 2.9–6.0</td>
</tr>
<tr>
<td>CD8+ activated by cross-linked anti-CD3+IL-2</td>
<td>CD28+CD11b−CD11b+: 17.7–32.4, CD28+CD11b+: 0.84–33</td>
<td>7.7–18.9 20.5–34.0</td>
</tr>
<tr>
<td>CD8+ activated by cross-linked anti-CD3+IL-2</td>
<td>CD28+CD11b−CD11b+: 7.6–24.2, CD28+CD11b+: 7.7–18.9</td>
<td>7.8–12.9 8.9–35.9</td>
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</table>

*aAutologous PMN of healthy donors were incubated for the times indicated; the percentage of CD66b and MHC class II-positive cells was measured by FACScan; the values represent the range obtained for the five individuals (expression of MHC class II immediately after isolation was <2% of the PMN in all experiments).
indicating T-cell activation but also discriminates between recently activated effector cells and memory cells [34, 35]. Indeed, in our patients with active disease, a small but conspicuous population of CD8+CD28+CD11b+ cells appeared. Expansion of such CD8+CD28+CD11b+ T cells has been reported before in patients infected with a virus [34]. Although, virus-infection (e.g. with CMV or EBV) could not be ruled out in our patients, we think that it is rather unlikely, because there were no clinical indications of virus infection, and 9 of the 10 patients had newly diagnosed disease and were not undergoing immunosuppressive therapy. Moreover, from in vitro experiments it is known that CD11b up-regulation is not specific for virus-infection, but occurs regularly in the course of T-cell activation [61].

CD8+CD28+CD11b+ cells are considered to be a transient ‘intermediate’ phenotype in the process of CD8+ activation, giving rise to the more persistent phenotype CD8+CD28−CD11b+ [36], which is found in patients in remission or under immunosuppressive therapy as well as in healthy donors. The percentage of these cells increases with age, most probably reflecting a history of previous activation, and the fact, that—in contrast to activated CD4+CD8+ are rather resistant towards apoptosis, and thus accumulate over a lifetime (reviewed in [62]).

Activation and expansion of CD8+ cells in the course of the active disease, combined with their higher resistance to apoptosis, could account for the shift of the CD4:CD8 ratio towards CD8+, the more so since CD4+ cells are lost [44].

In combination, our data provide evidence for the activation-induced expansion of CD8+, apparent as CD8+CD28+CD11b+. Ex vivo, these cells produce IFNγ. Following immunosuppressive therapy, IFNγ production is no longer apparent. It is of note, however, that IFNγ production is not limited to CD11b+ cells.

According to our hypothesis, PMN are activated by IFNγ derived most likely from the activated CD8+ cells. To test this more directly, CD8+CD28+CD11b+ cells were generated from healthy donors, because the use of patient-derived cells was precluded by the fact that autologous PMN would be required, which during active disease, however, are already activated. Therefore, T cells of healthy donors were used. With a cell line consisting of >90% CD8+CD28+CD11b+ cells, MHC class II expression on PMN could be induced. Similarly, T cells activated by a one-step exposure to anti-CD3, which up-regulated CD11b expression on the CD8+CD28+ cells, induced MHC class II on the PMN, as did the supernatants of activated T cells.

Triggering PMN with antibodies to PR3 in concentrations reported to affect the oxidative burst [8] had no effect at all on MHC class II expression, implying that the up-regulation of MHC class II antigens on PMN, as it is seen in vivo in patients with active disease, is not due to stimulation with anti-PR3, but rather to the action of activated T cells.

Whether or not the acquisition by PMN of MHC class II is of any relevance for the progress of the disease cannot be decided as yet. Other IFNγ-induced alterations of PMN, such as prolonged lifespan or enhanced cytotoxicity, are easier to reconcile with a pathogenetic role of PMN [46–49]. On the other hand, we and others [20, 23, 63] have shown, that MHC class II-positive PMN also serve as accessory cells for T-cell activation, which in turn could sustain the T-cell activation and thereby perpetuating the immune response.

Conclusion

In summary, this study provides evidence that T lymphocytes, particularly IFNγ-producing CD8+CD28+CD11b+ cells, expand during active disease. We propose that these T cells—as they do it in vitro—induce the differentiation of PMN which is typically seen in active disease, and that these altered PMN participate in the chronic-destructive inflammatory process.

Rheumatology key message

- During active primary vasculitis, IFNγ-producing CD8+CD28+CD11b+ T cells expand. These T cells—as they do it in vitro—might induce the differentiation of PMN, which is typically seen in active disease. These altered PMN might participate in the chronic-destructive inflammatory process.

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