Review

T cells in systemic sclerosis: a reappraisal

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Abstract

SSc is an autoimmune disease characterized by inflammation and extracellular matrix deposition that ultimately leads to loss of organ function. T cells appear to play a prominent role in its pathogenesis. The evidence for this comes from their being at the site of fibrosis, their activated phenotype and alteration in their number and frequency in peripheral blood. This review examines the role of T cells in the pathogenesis of SSc and specifically examines the key soluble profibrotic mediators (IL-4, IL-6, IL-13) secreted by Th2 cells and their interactions with fibroblasts that deposit excess extracellular matrix leading to fibrosis. We finally examine possible therapeutic options in targeting T-cell mediators to disrupt the cellular interactions between T cells and fibroblasts that serve to drive the fibrotic response. One of the factors driving fibrosis is IL-6 and this can be neutralized in vivo not only to limit IL-6-driven tissue fibrosis but concomitantly to suppress switching of Tregs to Th17 T cells that will provide more IL-6, thus perpetuating the fibrosis. Taken together, these data implicate the role of T cells in SSc and suggest that Th2-polarized T cells and the fibrotic mediators subsequently released directly induce fibrosis. Targeting such cytokines may be therapeutic not only in SSc but more generally in diseases where fibrosis is directed by inflammatory signals.

Key words: systemic sclerosis, autoimmunity, T cells, fibrosis, IL-6, tocilizumab.

Introduction

SSc is an idiopathic CTD that is characterized by the presence of autoantibodies, inflammation, vascular abnormalities and fibrosis of skin and inner organs. Raised inflammatory markers such as CRP or IL-6 in peripheral blood are typically observed in early phases of the disease, with the final result being excessive extracellular matrix material deposition, primarily collagen types I and III. Affected skin is infiltrated by mononuclear cells, mainly macrophages and activated T cells. The cell infiltration correlates with skin thickening, suggesting a relation between inflammation and fibrosis [1]. A definite cause for this inflammation has not been established but is similar to other autoimmune diseases; loss of tolerance to self-antigens, failure to resolve inflammation or both are thought to be involved [2].

Activation of the innate and acquired immune system is of importance in the early stages of the disease. This is shown by mast cell infiltration and degranulation, macrophage infiltration and an activated phenotype of circulating monocytes in the peripheral blood [3, 4]. Furthermore, autoantibodies such as anti-centromere and anti-ScI70 or against other targets are associated with disease subtypes and can predict disease progression [5].

Substantial progress in the knowledge of T-cell differentiation has been achieved in the past two decades (Fig. 1). In SSc, differentiation towards Th-2 lymphocytes has been reported [6]. This review examines the role of T cells in SSc with a specific focus on the role of T-cell-derived mediators that are pro-fibrogenic. A greater understanding of the interplay between T cells, their pro-fibrotic mediators and fibroblasts will contribute to improved drug development.

Animal models in SSc and T-cell activation

One of the most convincing lines of evidence for a role of immune cells in skin fibrosis comes from the fact that adoptive transfer of bone marrow cells from tight skin (Tsk) mice, an animal model of SSc, transferred to wild-type littermates, leads to skin fibrosis and increased transcription of collagen [7]. Indeed, in the Tsk mouse model of fibrosis genetic ablation of intercellular adhesion molecule-1 (ICAM-1) in this animal model reduced both the...
number of T cells infiltrating skin and also IL-6 levels, at the same time reducing fibrosis. Moreover, depletion of CD3+ T cells attenuates bleomycin-induced fibrosis, an induced model of SSc [8]. Similarly, in a radiation-induced rat model of pulmonary fibrosis, selective depletion of CD4+ Th cells before radiation resulted in less pulmonary fibrosis, thus indicating a prominent role of Th cells in driving the fibrogenesis [9]. The bleomycin model of fibrosis mimics the inflammatory changes observed in SSc, including the influx of T and B cells that leads to the production of fibrotic mediators.

**Clinical data**

The notion that T cells are involved in SSc is exemplified by the fact that treatment of a SSc patient with the humanized mAb alemtuzumab, targeting CD52, leads to a rapid and substantial clinical improvement [10]. Stratton et al. [11] demonstrated using anti-human thymocyte globulin a reduction in skin score and clinical improvement. Indeed, T cells have been shown to be a requirement for an anti-topo I antibody response [12]. Treatment with basiliximab, an anti-CD25 antibody (the high affinity IL-2 receptor) in SSc patients also resulted in improvement of skin thickening and pulmonary function, suggesting that T-cell targeting is a treatment option [13]. Further evidence comes from studies using CYC and autologous stem cell transplantation with preceding lymphoablation to reset the immune system [14, 15].

**Histology and cytology in SSc**

Skin biopsies taken from SSc patients contain perivascular infiltrates consisting of T cells (Fig. 2) and macrophages mainly in early disease 1, before microscopic evidence of fibrosis [16, 17], which suggests they play a role in the initiation of disease. Collagen content appears to be higher in fibroblasts adjacent to leucocytes. Moreover, SSc skin but not control skin expresses more ICAM-1 and has a higher *in vitro* propensity to recruit/adhere T cells to the tissue [18]. Expression of CD69, considered an early T-cell activation marker, was found to be increased in T cells from skin biopsies from patients [19]...
along with an increase in peripheral blood CD4+ T-cell activation markers [20]. There also appears to be a reduction in Treg cells in skin biopsies from SSC patients [21], suggesting altered capacity for immune regulation. A recent study has shown altered percentages of CD4+ memory phenotype in SSC patients [22].

Polarization of T cells in SSC

After activation, CD4+ T cells show remarkable plasticity to respond to the cytokine milieu with distinct effector functions. Early studies identified two Th cell subtypes: Th1 producing IFN-γ and Th2 subtypes producing IL-4, IL-5 and IL-13 [23]. Further work established that a Th1-skewed response promotes removal of intracellular pathogens and a Th2-polarized response is necessary for effective removal of helminth infections and induces IgE immunoglobulin production. A panoply of cytokine and transcription factor-specific networks help shape the CD4+ Th-cell response after activation via antigen presentation cells. Th-1 cell development is initiated by signal transducer and activator of transcription (STAT) 3 after IFN-γ and IL-17, which subsequently induces the transcription factor T-Bet, a master transcriptional regulator. In Th2 differentiation, STAT6 is activated by the critical cytokine IL-4, thereby directing the orchestration of GATA3, a master regulator, leading to transcription of IL-4, IL-5 and IL-13. There is also an autocrine loop of IL-4 (and also IL-13) on STAT6 leading to positive feedback and maintaining the Th2 bias.

Although many autoimmune diseases have a Th1-type preponderance, SSC has a predominant Th2 polarization; the reasons are unknown. However, it has been suggested that evolutionary pressure has evolved a Th2-type response as a rapid tissue repair response to tissue destructive pathogens [24]. Compelling evidence for a Th2-mediated tissue healing response comes from a colonic punch biopsy in mice that had delayed wound healing if their Th2 response was impeded [25]. In fact, Th2 cells can themselves instruct monocytes to differentiate into a specific dendritic cell subset that has high IL-10 and CD275 expression [26]. CD275 can promote IL-4 responses and IL-10 has been implicated in the repression of Th1 polarization.

T cells and co-stimulation

The ability of T cells to discriminate self from non-self antigens is critical to the normal functioning of the immune system. This is accomplished by positive and negative selection of T cells during thymic education [27]. Positive selection of T cells occurs as double-positive T cells that can recognize self-antigen MHC weakly are positively selected, whereas T cells that recognize self-antigen MHC strongly are negatively selected; this includes clonal deletion of T cells bearing self-reactive T-cell receptors and anergy [28]. Anergy is defined as a T-cell state of hyporesponsiveness [29]. Anergic T cells do not proliferate or secrete IL-2, and this helps to keep T cells from responding to autoantigens [29]. Autoimmunity arises when the mechanisms that maintain self-tolerance are broken.

Evidence for a genetic predisposition in the breakdown in tolerance in SSC comes from a study that identified the association of a genetic variant of CD226 (Ser307) in SSC patients compared with controls [30]. CD226 [also called DNAX accessory molecule-1 (DNAM-1)] is a 65 kDa glycoprotein of the Ig superfamily that is constitutively expressed on T cells and acts as a co-stimulatory molecule [31] involved in naïve T-cell differentiation [32]. The cell surface ligands are the poliovirus receptor (CD155) and nectin-2 (CD112), and both proteins are concentrated in adherens junctions [33].

CD226 plays a critical role in the development of murine graft-vs-host disease (GVHD) and its blockade attenuates T-cell activation and disease severity [34]. This is important, as GVHD is clinically similar to SSC and shares common features.

There is also evidence for functional and numerical changes of Tregs in SSC. These Foxp3-positive CD4+CD25+ T cells secrete anti-inflammatory cytokines including TGF-β and IL-10. Tregs are indispensable for immune tolerance. Depletion of Tregs not only promotes autoimmunity but also augments responses to non-self antigens. Alterations in frequency and number of Treg cells have been observed in several human autoimmune diseases, including RA and SLE [35], and mice lacking Treg cells develop spontaneous multi-organ autoimmune diseases. Interestingly, TNF-α has been shown to down-regulate the suppressive capacity of Tregs, mediated through ligation of TNF-R2, and inhibition of TNF-α with infliximab has been shown to restore their suppressive capacity [36]. In SSC, TNF-α levels are reportedly elevated, thus elevated TNF-α could reduce the suppressive capacity of Tregs. Klein et al. [37] showed that although overall the absolute number of peripheral blood Tregs was not different in SSC patients from healthy controls, there were fewer Tregs in SSC skin biopsies, suggesting an attenuated immunomodulatory response. In another study, however, an increased frequency of Treg cells was detected in peripheral blood of SSC patients, which correlated with disease activity [38]. However, this Treg population expansion was not associated with a functional decline in Tregs. Radstake et al. [39] also found an increased overall number of Tregs in SSC patients, which with a diminished functional capacity to suppress effector CD4+ T cells and that this Treg-diminished functional capacity is dependent on a serum factor that was not identified.

Th2 bias in SSC

There are reports of high levels of Th2 cytokines in SSC serum such as IL-4 and IL-13 [40]. IL-4 is critical in polarizing the Th2 response mediated through its receptor and STAT6. However, IL-4 does not work alone and IL-13 is also necessary to mount an appropriate Th2 response. Where is the initial IL-4 and/or IL-13 that drives Th2 polarization coming from? Linking the innate and adaptive arms of the immune system, maybe IL-4 and IL-13 are secreted...
by monocytes and macrophages. Monocytes are activated in SSc, and monocyte-lineage cells may be one of the first cell types to initiate the immune response, directing the T cell to make a lineage choice through the secretion of IL-4 and IL-13, thereby promoting Th2 differentiation.

Th2 T-cell helper cells would then work in a positive feedback loop perpetuating the phenotype and secretion of Th2-type fibrogenic cytokines. It is of note that alternatively activated macrophages help resolve inflammation and promote wound healing, and these macrophages are present in SSc skin biopsies [40]. Moreover, phenotypic markers of alternatively activated macrophages (CD204+ and CD163+) are elevated on CD14+ cells in SSc [4]. One interpretation of this data is that the alternatively activated macrophages are there to dampen inflammation and promote wound healing through the secretion of soluble factors, which promote differentiation of skin-infiltrating naïve T cells from Th0 to Th2. However, the initial priming of T cells probably occurs in lymph nodes.

**T-cell-derived cytokines drive fibroblast matrix deposition**

A characteristic feature of SSc is the presence of a persistent inflammatory infiltrate, including T cells, associated with regions of fibrosis and matrix remodelling. Fibrosis occurs when the homeostatic balance is altered between the deposition of extracellular matrix and the proteolytic breakdown of the matrix. Mediators that alter either the deposition or breakdown of the matrix will lead to a perturbation of matrix leading to fibrosis. The cellular and molecular factors that govern this alteration in matrix deposition remain largely unknown. There is currently a strong impetus to identify factors that induce matrix deposition, with a major focus on TGF-β, however, we argue that the role of T-cell-derived cytokines is just, if not more, important. A widely held assumption is that monocytes are the predominant source of pro-fibrotic mediators responsible for fibrosis, however, Th2 cells are a potent source of pro-fibrotic mediators and elucidation of their co-operative roles will yield new drug targets.

Classic Th2 cytokines include IL-4, IL-5 and IL-13. IL-4 is a kDa-multifunctional cytokine produced by activated Th2 T cells. The gene for IL-4 has been found to be clustered on chromosome 5q, particularly close to IL-13 gene. It normally promotes humoral immunity by inducing immunoglobulin production and isotype switching and is involved in the differentiation of naïve CD4+ T cells towards a Th2 phenotype [41]. Antibody-mediated depletion of CD3+ T cells in bleomycin mice decreased fibrosis along with reduced IL-4 secretion [42]. Elevated levels of IL-4 have been demonstrated in SSc tissue both at the mRNA level and protein level [43]. Luzina et al. [44] have demonstrated that CD8+ cytotoxic T cells are activated and secrete high levels of IL-4 in SSc patients. Moreover, IL-4 has been shown to induce tenasin, a large extracellular matrix protein, in both normal and SSc fibroblasts. Also direct stimulation of human fibroblasts with IL-4 leads to a significant increased expression of collagen and fibronectin, and SSc-derived fibroblasts are more sensitive to such induction [45]. In the Tsk model, treatment with antibodies against IL-4 prevented the induction of dermal fibrosis [46]. The Tsk mouse harbours a chromosome 2 mutation that produces an increase in skin and internal organ deposition of collagen. Targeted mutation of the IL-4Rα gene in Tsk mice leads to attenuated skin fibrosis, collagen content and, interestingly, anti-topo I antibodies [47]. Indeed, elevated levels of IL-4 and IL-6 have been demonstrated in the sera of SSc patients [48], suggesting systemic release of IL-4. Some of the strongest evidence for a pro-fibrotic role of IL-4 is the fact that genetic deletion of the IL-4 gene in mice subsequently challenged with bleomycin leads to reduced fibrosis and fibroblast collagen production compared with wild-type animals [49]. Indeed, it has been demonstrated that both IL-4-secreting cells (T cells) and CD40 ligation on the fibroblasts drives a synergistic increase in fibroblast activation and proliferation [50]. This suggests that as well as the pro-fibrotic effects of IL-4, cells expressing CD40 ligand (CD154) help synergize the activation response. CD154 is primarily expressed on activated T cells and is found in greater abundance in CD4+ Th cells in the peripheral blood of SSc patients [51]. Indeed, anti-CD154 antibodies suppress skin fibrosis in the bleomycin animal model of fibrosis, and this was, at least partly, dependent on blockade of monocyte chemotactic protein-1 (MCP-1) and RANTES.

IL-13 is an immunoregulatory cytokine also produced predominantly by activated Th2 cells. IL-13 is an important mediator in the pathogenesis of asthma and airway remodelling [52]. IgE antibody production and mastocytosis, and is directly pro-fibrotic. IL-13 shares many functional activities with IL-4 because both share a common IL-4Rα chain receptor and signal through STAT-6 [53]. Although both IL-4 and IL-13 have similar and overlapping functions they both have non-redundant functions [54]. IL-4 is important for polarization of naïve CD4+ T cells. IL-13, however, is not necessary, as IL-13Rα1 has not been demonstrated on T cells. Indeed, IL-13 was found to be directly fibrotic in a hepatic fibrosis model, and depletion of IL-13 was associated with much reduced fibrosis and collagen deposition; it was clear from the double IL-4−/−IL-13 knockout mice that IL-13 was the predominant pro-fibrotic mediator in a natural model of hepatic fibrosis induced by infection with Schistosoma mansoni [54]. Interestingly, in the same infection hepatic fibrosis model IL-13-dependent fibrosis was evident, yet was TGF-β and Smad-3 dependent [55], thus indicating that IL-13 is directly driving fibrosis that is independent of the classic TGF-β pathway of fibrosis [56]. Targeted pulmonary overexpression of IL-13 using genetic approaches in mice results in lung fibrosis [57]. Using the bleomycin model of SSc it was demonstrated that IL-13 is increased in the pathogenesis of the disease and neutralization with IL-13 antibodies attenuates this effect [58]. In both normal and keloid fibroblasts, IL-13 resulted in direct up-regulation of collagen production that was similar in magnitude to TGF-β-stimulated...
production [59]. Addition of IL-13 also reduced MMP levels and increased tissue inhibitor of metalloprotei nease 1 (TIMP-1) expression, thereby altering the extracellular matrix remodelling in favour of increased deposition [59]. IL-13 has also been shown to be an absolute requirement for the development of cutaneous fibrosis mediated by IL-33, as genetic deletion of IL-13, but not of IL-4, totally abrogates IL-33-mediated fibrosis and collagen content, and this was independent of TGF-β1 expression [60].

**CD4CD8 double-positive T cells are high pro-fibrotic cytokine producers**

Of particular note recently has been the identification of an unusual subtype of CD4+CD8+ double-positive T cells in the skin of SSc patients that secrete very large quantities of IL-4 [61]. Interestingly, as well as CD4+CD8+ double-positive T cells, CD8+ single-positive T cells had increased levels of IL-4 compared with CD4+ single-positive populations in SSc patients [61]. This increase in CD8+ single-positive T cell IL-4 secretion was also found in a previous study from lung bronchoalveolar lavage fluid that was associated with a significant decline in lung function over time, indicating it plays a direct pathogenic role [62]. More recently CD8+ single-positive T cells from SSc patients were shown to have an elevated propensity towards IL-13 secretion after *in vitro* T-cell activation, which was correlated with the extent of skin thickening [63]. Furthermore, this CD8+ T cell-secreted excessive IL-13 was dependent on a transcription factor GATA-3, as siRNA knockdown of GATA-3 greatly reduced IL-13 levels [64]. The data suggest GATA-3 could be a therapeutic target in SSc, as inhibition of the central transcription factor would (i) inhibit differentiation of naïve T cells to Th2-polarized T cells and thus diminished production of pro-fibrotic mediators and (ii) inhibit already differentiated Th2 T cells from secreting IL-13 directly after differentiation.

**IL-6 in the mix**

IL-6 is a classic inflammatory cytokine produced by T cells and many other cells as part of the acute phase response [65–67]. Historically described as a pro-inflammatory mediator, this cytokine has been demonstrated to be involved in immune regulation, haematopoiesis, oncogenesis and fibrosis. Pleotropic IL-6 signals by binding to the IL-6R α chain and the signal transducing component gp130 (CD130) and interacts with janus kinases after tyrosine phosphorylation to produce downstream signalling events mediated by STAT1 or STAT3. Although it has many physiological effects, IL-6 is also implicated in many autoimmune diseases including RA and JIA. In addition to its classic role as a pro-inflammatory mediator it is also directly fibrotic. Cultured peripheral blood mononuclear cells (PBMCs) from SSc patients produce high levels of IL-6 *in vitro* compared with healthy controls [68]. Serum levels of IL-6 are elevated in SSc and are significantly correlated to skin thickness [40, 69]. Furthermore, IL-6 levels have been found to be elevated in SSc patients’ bronchoalveolar lavage fluid compared with controls [70]. In mice treated with topo I with complete Freund’s adjuvant, to induce an anti-topo response, mice developed an autoimmune disease with SSc-like skin thickening and lung fibrosis while knockdown of IL-6 ameliorated this SSc-like pathology, thus IL-6 is a critical signalling molecule in SSc [71]. Genetic deletion of the IL-6 gene in mice results in an attenuated fibrotic response after bleomycin challenge which may be associated with a reduced TGF-β1 expression pattern [72]. Increased expression of IL-6 has been demonstrated by immunocytochemistry in lesional skin of SSc patients and was associated with the later stage of disease [73, 74]; indicating it plays a role in the extracellular matrix deposition.

Barnes et al. [75] have demonstrated that IL-6 signalling mediates endothelial activation and apoptosis in SSc, which could then lead to the secretion of endothelial-derived cytokines into the local tissue microenvironment and hence perpetuate the fibrosis. Also, IL-6 drives the differentiation of CD4+ T cells into IL-4-secreting Th cells [76], thus positively driving the Th2 T-cell pool and thereby perpetuating the pro-fibrotic response.

Using a mouse anti-human-IL-6 antibody, Kawaguchi et al. [77] demonstrated attenuated collagen I levels in dermal fibroblasts derived from SSc donors compared with non-specific antibody. Intriguingly, a recent study using the bleomycin model demonstrated that IL-6 knockout mice had much reduced inflammation and fibrosis, and using an anti-mouse IL-6 receptor-specific antibody not only improved, but prevented, fibrosis [78]. This accrual of evidence clearly implicates IL-6 in fibrosis. Fig. 3 demonstrates a possible pathway of T-cell-driven fibrosis, with mediators binding to their cognate receptors leading to excess matrix deposition. Fibroblasts do not express the IL-6 receptor, they only express the gp130 subunit, so cannot respond to IL-6. However, a process termed trans-signalling can occur in which cells that do not express the IL-6 receptor can signal through an association between soluble IL-6 receptor, IL-6 and the ubiquitously expressed gp130 subunit. The IL-6 receptor is sparsely expressed, so IL-6 trans-signalling significantly increases the number of IL-6 responsive cells, due to widespread expression of gp130. It is of interest that soluble IL-6 receptor levels are elevated in PBMCs of SSc patients [68]. This suggests that cleavage of the soluble form of the receptor increases the range of cells capable of transducing the IL-6 signal and that soluble IL-6 receptor concentrations are critical in mediating its effects. As well as driving the transcription of matrix genes such as collagen I, thereby leading to fibrosis, IL-6 also renders the cells resistant to apoptosis. It is also of interest that the cleavage of the IL-6R is mediated by the metalloprotease ADAM17 (sheddase), and this is induced by CRP [79]. Thus pathophysiological relevant concentrations of CRP likely to be encountered in SSc have the potential to alter IL-6 signalling through modulation of the soluble IL-6 receptor complex by eliciting proteolytic cleavage of IL-6 receptor. Therefore, T cells not only supply pro-fibrotic cytokines in the local microenvironment to augment...
fibrosis but also supply the soluble receptor to the cells that lack IL-6 receptor thereby rendering them responsive. Indeed, the activation status of the T cells may lead to alterations in soluble IL-6R and determine responsiveness to exogenous IL-6.

Th17 cells are a distinct class of effector T cells, characterized by high IL-17 expression. They have a lineage distinct from that of Th1/Th2 cells. Recent observations have shown that Th17 cells are associated with numerous diseases, including RA, in which high frequencies of this...
subpopulation are found. Interestingly, a recent report has shown that Tregs, there to suppress an aberrant immune response, can be converted to Th17-secreting cells only when in the presence of IL-6 (or IL-1β) [80]. One could speculate that in the relatively high IL-6 environment of the affected organ in SSc, Tregs within the local microenvironment are switched to Th17 cells, thus releasing further pro-inflammatory mediators and pro-fibrotic molecules perpetuating the fibrosis. This switching under the optimum conditions may explain the reduced Tregs demonstrated in SSc.

Conclusions

SSc is an autoimmune disease in which T cells respond to an unknown antigen and differentiate to a Th2-type response. This Th2 polarization leads to many cytokines that are themselves driving increased extracellular matrix in the organs affected. It is clear that cytokines such as IL-4, IL-13 and IL-6 are secreted in large quantities in SSc and they are promoting fibrosis, either directly or indirectly. These pro-fibrotic cytokines, either alone or in combination, may also act as perpetuators of IL-6 secretion from the resident fibroblasts that then act in an autocrine manner within the local microenvironment. Whether cytokines such as IL-6, IL-4 or IL-13, or all three, are pivotal in SSc pathogenesis can now be tested in clinical trials. It is interesting to note that a recent clinical trial in SSc using imatinib, a tyrosine kinase inhibitor, resulted in significant reduction in IL-4-producing CD4⁺ T cells, but not total CD4⁺ T cells [81]. It is possible that imatinib is redirecting a Th2 to a Th1 response in SSc. Furthermore, inhibition of the central transcription factor, GATA-3, that underpins IL-13 secretion and naive T-cell differentiation appears an attractive therapeutic target. Neutralization of IL-6 would also alter the balance between Th17 and Tregs, as IL-6 both promotes naive Th cell Th17 differentiation, inhibits TGF-β-induced Treg differentiation and also switches Tregs to inflammatory IL-17 producing Th17 [82]. Table 1 indicates therapeutic antibodies that could be used in SSc.

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Clinical vignette

Giant cell arteritis followed by idiopathic retroperitoneal fibrosis in the same patient—an unexpected positron emission tomography finding

A 78-year-old male patient was diagnosed with GCA, confirmed by positive histology of the temporal artery. Treatment with prednisone 1 mg/kg of body weight was initiated, tapered and stopped after 2 years. Two years later, with unremarkable regular controls, the patient presented with lumbar pain, elevated ESR (41 mm/h) and CRP (27 mg/l). PET-CT scan (Fig. 1A) was performed, showing moderately elevated fluoro-deoxy-glucose (FDG) uptake in both femoral arteries and a retroperitoneal metabolically active mass partially obstructing the left urether. MRI scans of the abdomen (Fig. 1B) were consistent with the diagnosis of idiopathic retroperitoneal fibrosis (IRF) with left-sided grade I hydronephrosis. IgG4 was initially elevated to 2.00 g/l (normal range 0.08–1.4 g/l) subsiding to 0.62 g/l under treatment with prednisone (1 mg/kg body weight). With 5 mg of prednisone per day, both diseases have remained inactive for the past 6 months.

This case describes a patient suffering from both GCA and IRF, an IgG4-related sclerosing disease often associated with elevation of the IgG4 subclass. IRF has not yet been described in patients with GCA. However, similarities in histopathology with inflammation in the medial and adventitial layers of the aorta suggest common yet unproven pathogenetic mechanisms for IRF and GCA.

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(A) The PET scan shows focal FDG enhancement periaortal at the level of the aortic bifurcation (difficult to discriminate from the adjacent urether) and retention of nuclide activity due to hydrenephrosis. (B) The transverse MRI of the abdomen with gadolinium-enhanced T1-weighted, fat-saturated fast spin echo shows marked periaortic uptake of contrast material just proximal to the aortic bifurcation.