Larger abdominal aortic aneurysms (AAAs) have a high propensity to rupture, which makes them a significant health problem. As a result, elective repair is generally recommended. However, the great majority of AAAs are small and do not establish such a risk, in particular, not if the growth of small AAAs is absent. It has been pointed out that pharmaceutical interventions, which stabilize small AAAs and thus reduce the need for surgical repair, could be highly beneficial. Yet, the most effective strategies still have to be identified.

The pathology of larger AAAs is complex and best described as a general proinflammatory response and an accompanying proteolytic imbalance, the latter being held responsible for the excess matrix turnover in the disease. The inflammatory fingerprint of the larger AAA is multifaceted and is characterized by marked interleukin (IL) 6 and IL-8 hyperexpression, and by a comprehensive cellular infiltrate that includes ample macrophages, B cells, T cells, plasma cells, neutrophils, mast cells, and other cell types. Yet, the role of these inflammatory cells in perpetuating aneurysm progression is still far from clear.

Here, we present the histology of an anterior-lateral aneurysm wall sample from a 72-year-old woman who underwent emergency repair because of a ruptured AAA. At 69 years of age, the patient received a kidney transplant because of kidney failure (membranous glomerulonephritis). On transplantation, she received a protocolized immunosuppression regimen (prednisone, 7.5 mg/d; cyclosporine, 75 mg BID [area under the curve 1957 ng · h⁻¹ · mL⁻¹]; and mycophenolate, 500 mg BID). During the workup for transplantation (ie, 34 months before the rupture), a 3.4-cm AAA was diagnosed (Figure 1A and Figure 2). The patient refused follow-up of her AAA, and no follow-up scans were performed. On a computed tomography scan performed 4 months before the rupture, the AAA had increased to 7.0 cm (Figure 1C and Figure 2). During the workup for surgical AAA repair, the patient presented with a ruptured aneurysm (27 months after the kidney transplant). She underwent an
uneventful open emergency repair. The patient recovered well, and renal graft function was preserved.

The observed rapid AAA progression (ie, 13 mm/y) and ultimate rupture under an intense immunosuppressive regimen is remarkable, in particular with respect to the alleged critical role of inflammation in the perpetuation of AAA disease. To evaluate the inflammatory response in the aneurysm wall, we conducted a histological analysis of T cells (CD3), T-helper cells (CD4), cytotoxic T cells (CD8), B cells (CD20), macrophages (CD68), neutrophils (myeloperoxidase staining), mast cells (tryptase), and smooth muscle cells (α-smooth muscle actin) on tissue sections from the nonruptured area of the patient’s AAA. The results of this analysis showed an abundance of all cell types in a control AAA, but the complete absence of T cells, B cells, and neutrophils in the aneurysm wall of the patient (Figure 3). Macrophages (Figure 3) and smooth muscle cells and mast cells (not shown) were abundantly present and apparently not influenced by the immunosuppression. In addition to the staining, we also performed semiquantitative real-time polymerase chain reaction on duplicate samples of the patient’s aneurysm wall, and compared the results with those of 10 ruptured AAAs from AAA patients without immunosuppressive drugs (controls). This evaluation showed a 13-fold reduction in aortic wall interferon γ expression in the patient, but collagen type I and III; IL-6, IL-8, and tumor necrosis factor α; and matrix metalloproteinase types 2 and 9 and cathepsin K, L, and S mRNA levels appeared highly similar in the patient and controls.

The observed aggressive course after the kidney transplant (Figure 2) in this patient fits well with earlier reports of accelerated AAA progression and unexpectedly high rupture rates in patients that have undergone solid-organ transplantation, and it suggests a profoundly more malicious course of the disease in these patients. The aggressive natural history of AAA disease in patients receiving an intense immunosuppression regimen appears highly counterintuitive. A large body of (preclinical) evidence points to the crucial role of both the adaptive immune system and neutrophils in the perpetuation of AAA disease. Observations from this single patient demonstrate that the immunosuppressive regimen results in complete absence of aneurysm wall T and B cells and neutrophils, as well. These cell types are all considered instrumental in the perpetuation of AAA disease. Rapid AAA progression and rupture in this patient, and reports on aggressive AAA progression in other patients receiving a solid-organ transplant, as well, even suggest that immunosuppression may have an adverse effect on AAA progression.
Although accelerated AAA growth and rupture in the patient may reflect the effect of steroids on the matrix turnover, the maintenance dose used in the patient was modest. We quantified the number of smooth muscle cells and assessed collagen type I and III mRNA expression levels in the patient, and found results that closely matched the mean expression level of the 10 control aneurysms without immune suppression. Another explanation is that, contrary to the general belief, the adaptive immune response in AAA should be considered protective, either in respect to modulation of macrophage activity or proteolytic pathways, or with regard to matrix homeostasis.5

Antiinflammatory interventions are now considered one of the most promising pharmaceutical strategies for the medical stabilization of growing AAAs. This case, along with the previous reports on the aggressive clinical behavior of AAA in patients with a solid-organ transplant, questions the current hypothesis of the basis of the pathophysiology of AAA disease. It also shows that antiinflammatory interventions in AAA could be potentially harmful and should be carefully monitored.

Disclosures
None.

References
Immunosuppression and the Abdominal Aortic Aneurysm: Doctor Jekyll or Mister Hyde?
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