

Case report

ANCA-positive vasculitis as a secondary autoimmune disease after autologous stem cell transplantation for systemic sclerosis: a case report

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ABSTRACT

Autologous stem cell transplantation (SCT) is increasingly used to treat autoimmune diseases (AD), in particular systemic sclerosis (SSc). Secondary autoimmune diseases are a known complication after autologous stem cell transplantations for any cause. A 43-year-old man had received an autologous stem cell transplantation for an aggressive diffuse cutaneous SSc. After mobilisation with cyclophosphamide and Granulocyte-Colony-Stimulating Factor stem cells were CD34-selected. The patient received a conditioning regimen with cyclophosphamide and Antithymocyte globulin. He had an excellent response with the modified Rodnan Skin Score decreasing from 34 to 3. One year and 4 months after SCT mild erythrocyturia without acanthocytes and proteinuria were seen for the first time on routine urinalysis. During the following year erythrocyturia increased to 131 erythrocytes / μ l and protein excretion to 628 mg/g creatinine. At that time, acanthocytes of 25% finally could be detected. Due to the clearly nephritic constellation in urinalysis a renal biopsy was performed, which revealed mild global and focal-segmental sclerosing and focal-segmental proliferative glomerulonephritis without any signs of a IgA-nephropathy. The result was compatible with a renal manifestation of a small-vessel vasculitis. During the following laboratory workup ANCA of a perinuclear pattern with specificity for myeloperoxidase in high titers could be detected. Therefore the diagnosis of a p-ANCA-positive glomerulonephritis was established. As treatment, the patient received Rituximab, which turned out to be effective. We provide the first report of a patient who developed a p-ANCA-

associated vasculitis after autologous stem cell transplantation for an autoimmune disease, namely systemic sclerosis.

Case report

Autologous stem cell transplantation (SCT) is increasingly used to treat autoimmune diseases (AD), in particular systemic sclerosis (SSc) (13). Secondary autoimmune diseases are a known complication after autologous stem cell transplantations for any cause. Patients transplanted because of rheumatic diseases seem to be even more at risk to develop these phenomena.

We provide the first report of a patient who developed a p-ANCA-associated vasculitis after autologous stem cell transplantation for an autoimmune disease, namely systemic sclerosis. The patient consented to the publication of this article.

A 43-year-old man of Tunisian origin was seen on a regular basis in our rheumatology outpatients department after receiving an autologous stem cell transplantation for an aggressive diffuse cutaneous SSc. Before SCT autoantibody profile was negative apart from positivity for ANA and Scl-70 antibodies. In particular, ANCA were negative. The patient had a rapidly progressive cutaneous sclerosis under medication with imatinib, with the modified Rodnan Skin Score (mRSS) increasing to 34, polyarthritis, debilitating joint contractures and tendovaginitis. Thorough diagnostic work-up did not reveal any organ involvement, and no renal involvement in particular. For SCT stem cells were mobilised with Cyclophosphamide 2x2 g/m² and Granulocyte-Colony-Stimulating Factor (G-CSF). Stem cells were CD34-selected, and

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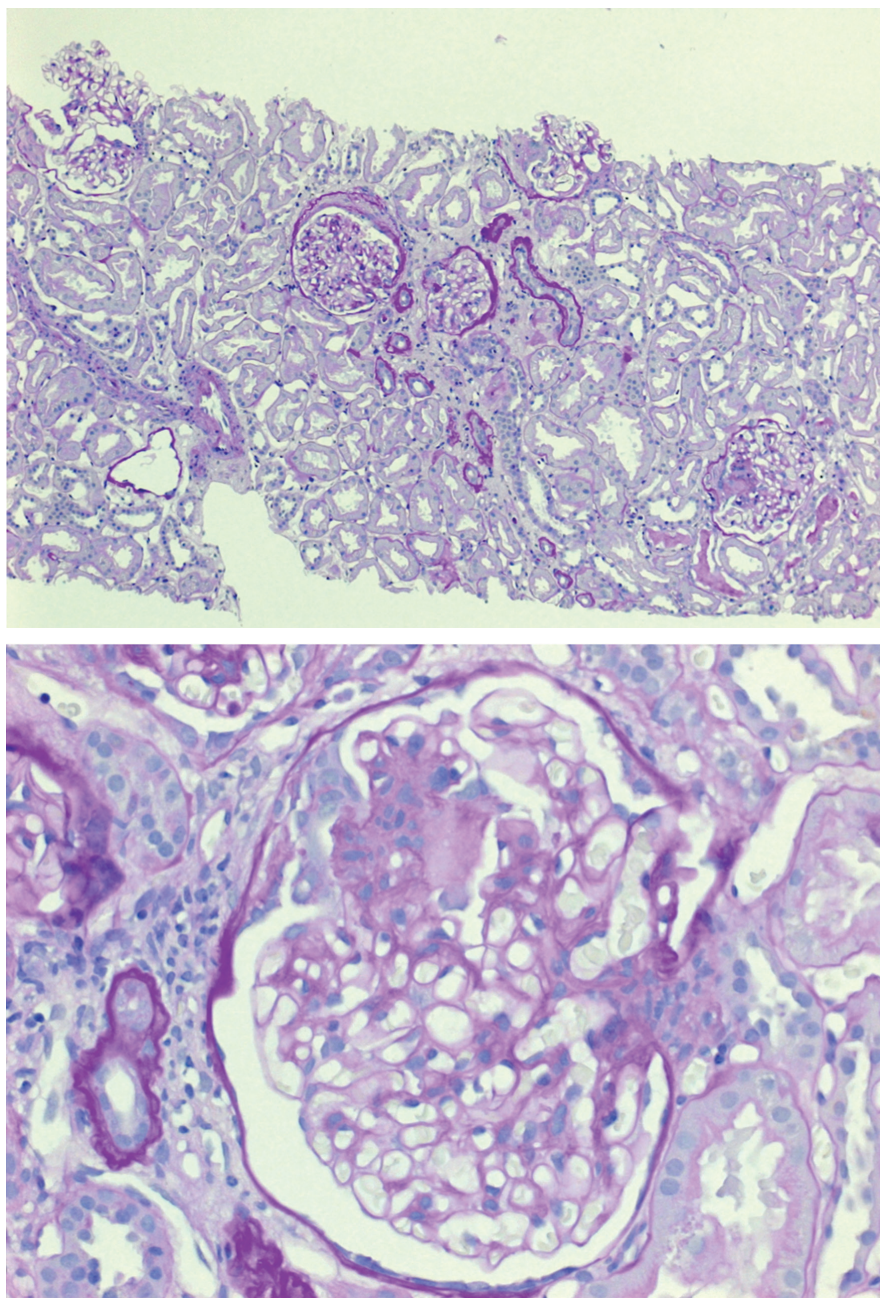


Fig. 1. Periodic Acid-Schiff (PAS) staining. Magnification: x 10 (1) and x 40 (2).

the patient received a conditioning regimen with cyclophosphamide 4x50 mg/kg and ATG (Fresenius) 4x10 mg/kg in September 2009. As a complication he developed a pulmonary aspergillosis, from which he quickly recovered with antimycotic therapy. He had an excellent response with the mRSS decreasing from 34 to 3 and complete normalisation of range of motion of all his joints. After transplantation no immunosuppressive therapy was conducted. In July 2012, two years and ten months after transplant methotrexate

was initiated due to slight progression of cutaneous sclerosis.

In January 2012, two years and 4 months after SCT mild erythrocyturia without acanthocytes and proteinuria were seen for the first time on routine urinalysis. A non-renal cause for erythrocyturia was first suspected due to the high cumulative dosage of cyclophosphamide the patient had received. Unfortunately the patient avoided urological counseling. During the following year erythrocyturia increased to 131 erythrocytes/ μ l and protein excretion

to 628 mg/g creatinine. At that time, in January 2013, acanthocytes of 25% finally could be detected. Nevertheless, renal function stayed within normal range.

Due to the clearly nephritic constellation in urinalysis a renal biopsy was performed, which revealed mild global and focal-segmental sclerosing and focal-segmental proliferative glomerulonephritis with one fresh and two old crescents (of 14 glomeruli) and mild mesangial hypercellularity without any signs of a IgA-nephropathy (Fig. 1). The result was compatible with a renal manifestation of a small-vessel vasculitis. During the following laboratory workup ANCA of a perinuclear pattern with specificity for myeloperoxidase in high titers could be detected for the first time. Therefore the diagnosis of a p-ANCA-positive glomerulonephritis was established.

In May 2013, the patient received rituximab (1000 mg on days 1 and 15), and his prednisolone dose was raised to 20 mg daily. A higher dosage of prednisolone was avoided due to the risk of renal crisis in SSc, and the dosage was thought adequate because of the slow progression of the glomerulonephritis without impairment of glomerular filtration rate or elevation of creatinine. The patient showed a rapid response with a considerable decrease of proteinuria from 628 mg/g to 268 mg/g creatinine. 4 weeks after the second infusion of rituximab acanthocyturia resolved. An evaluation 4 months after rituximab showed remission of glomerulonephritis under an ongoing treatment with 10 mg of prednisolone and methotrexate 15 mg weekly.

To our knowledge, this is the first case report of an ANCA-positive vasculitis as a secondary autoimmune phenomenon after autologous SCT for a rheumatic disease.

The differential diagnosis of glomerulonephritis being a renal manifestation of SSc was dismissed, since SSc itself showed no signs of progression, and an overlap of SSc with ANCA-associated vasculitis is rare (4). If against all odds such an overlap was the case in this patient, the course of the disease would still be remarkable, since the

SCT would have changed the disease pattern completely.

In a recent study, Daikeler *et al.* gave a comprehensive overview of secondary autoimmune diseases after autologous stem cell transplantation for AD reported to the EBMT. 29 of 347 patients developed at least one secondary AD. These comprised autoimmune hemolytic anaemia, acquired haemophilia, autoimmune thrombocytopenia, antiphospholipid syndrome, thyroiditis, blocking thyroid-stimulating hormone receptor antibodies, Graves' disease, myasthenia gravis, rheumatoid arthritis, sarcoidosis, vasculitis, psoriasis, and psoriatic arthritis (5).

Loh *et al.* published a monocentric study about secondary AD after autologous SCT for rheumatic diseases. Of 155 patients included in this retrospective analysis, six patients had a secondary autoimmune disease. In two patients a FVIII inhibitor was found. In the other four patients autoimmune cytopenias occurred (6).

In another study by Daikeler *et al.* patients from the EUROCORD registry were evaluated. Of the 726 patients who underwent cord blood transplantation for various primary diseases – but not rheumatic diseases – 52 developed

at least one AD, and namely one patient suffered from a membranous glomerulonephritis (7). Single cases of glomerulonephritis or ANCA positive vasculitis were described after autologous SCT for malignant diseases or allogeneic SCT. In 2002 Kingdon *et al.* published a case of p-ANCA positive vasculitis with renal and pulmonary manifestations after autologous SCT for non-Hodgkin lymphoma (8). In response, a case of p-ANCA and anti-GBM positive vasculitis following bone marrow transplantation for acute myeloid leukaemia was reported (9).

Therefore the constellation of primary disease and post-transplant complication in our patient is quite unique. A thorough follow-up of patients after autologous SCT for rheumatic disease is advisable which also should include urinary sediment with microscopy, urinary protein-creatinine ratio and autoantibodies.

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