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LETTER TO THE EDITOR

Necrobiotic xanthogranuloma successfully treated with autologous stem cell transplantation

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Abstract Paraproteinemia can be complicated by necrobiotic xanthogranuloma. Therapeutic options for this progressive disease are limited, and there is no agreement on a single best strategy. We report the case of a patient with a massive periorbital infiltration narrowing the palpebral fissure and blinding the patient. Conventional myeloma therapy had only limited benefit in our patient. However, he was successfully treated with high-dose chemotherapy followed by autologous stem cell transplantation, rendering the patient free of symptoms. This is the first report of autologous stem cell transplantation in a patient with necrobiotic xanthogranuloma.

Keywords Paraprotein · Necrobiotic xanthogranuloma · Hematopoietic stem cell transplantation · Autologous transplantation · Blindness

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Introduction

Necrobiotic xanthogranuloma (NXG) comprises characteristic xanthomatous skin infiltrates and subcutaneous nodules associated with paraproteinemia. On the skin, yellow, red-orange or violacious plaques or papules are observed, typically affecting the periorbital region. With decreasing frequency, the trunk, face, extremities, buttock and genitalia can also be involved. The degree of cutaneous manifestations is variable. Some patients are not disturbed at all; in others, the lesions are disfiguring, cause pain, chronic ulceration or mechanical complications such as blindness. Biopsy of cutaneous lesions reveals typical hyaline material of unknown chemical composition, distributed in a reticular pattern (necrobiosis). Necrobiosis and cholesterol clefts are surrounded by foamy macrophages and multinucleated giant cells (Touton cells). NXG is usually associated with paraproteinemia of the IgG, less frequently of the IgA class. In most cases, diagnostic criteria of multiple myeloma are not met. NXG is a rare condition; it was first described in 1980 [1]; since then, approximately 110 cases have been published [2, 3]. Treatment is based on myeloma therapy or follows anecdotal reports; a single best therapy has not been established [2–7]. We report the first case of successful autologous peripheral blood stem cell transplantation (PBSCT) in a patient with NXG.

Case presentation

A 26-year-old man presented to our hematology clinic in November 2001 with a 12-month history of indurated yellow palpebral skin infiltrations. Previously, two monotypic IgGκ peaks had been recognized on immunofixation of the serum; however, morphology and percentage of

plasma cells in the bone marrow were normal. Furthermore, chronic active hepatitis B with normal liver function tests and splenomegaly (17 cm) was reported. No therapy was initiated; the patient was followed closely. One year later, 23 months after the first symptoms, the infiltrates had progressed. The palpebral fissures were severely narrowed to a maximum of 3 mm at the left and 2 mm at the right eye. The patient was unable to work as a lorry driver. Paraproteinemia had slightly increased (Fig. 1a); the other hematological parameters had not changed. Biopsy of the periorbital lesions showed hyaline material with infiltrates of lymphocytes, plasma cells and foamy macrophages; necrobiosis was surrounded by giant cells of the Touton type (Fig. 1b,c). Based on the clinical and pathological findings, NXG was diagnosed. From October to December 2002, pulsed high-dose oral dexamethasone was applied [4]. To prevent exacerbation of hepatitis B, lamivudine had been started previously, which effectively suppressed the hepatitis B virus (HBV-DNA undetectable by PCR). Within a few days of dexamethasone treatment, the patient noted softening of the infiltrates; after several weeks, he was able to open his eyes. Clinical improvement was accompanied by a decrease in both M protein peaks (Fig. 1a). However, three months after the last dexamethasone dose, the condition relapsed. A trial of thalidomide was not tolerated by the patient because of severe fatigue. In 2003, paraproteinemia had progressed; skin infiltrates now also involved the penis and both nipples. Due to the palpebral indurations, the patient was now unable to open his eyes and literally blinded (Fig. 2a). A trial of interferon-α [6] was ineffective. In November 2003, weekly plasmapheresis was started [7]. Within a few weeks of treatment, there was both a decrease in paraprotein and a widening of the palpebral fissure. However, only 1 month after stopping plasma exchange, both eyes were occluded again. By October 2003, the patient was pancytopenic (hemoglobin 12.5 g/dl, thrombocytes 108×10^9/l, neutrophils 0.84×10^9/l). Splenomegaly had progressed to 22 cm. An adrenalin test [8] proved splenic pooling, prompting splenectomy. Histological work up showed diffuse infiltration of a low percentage of plasma cells. Florescence-activated cell sorting (FACS) analysis of splenic cells identified an IgGκ plasma cell clone (5% of cells). An IgGκ-clone was also discovered in the bone marrow, involving 5% of medullar

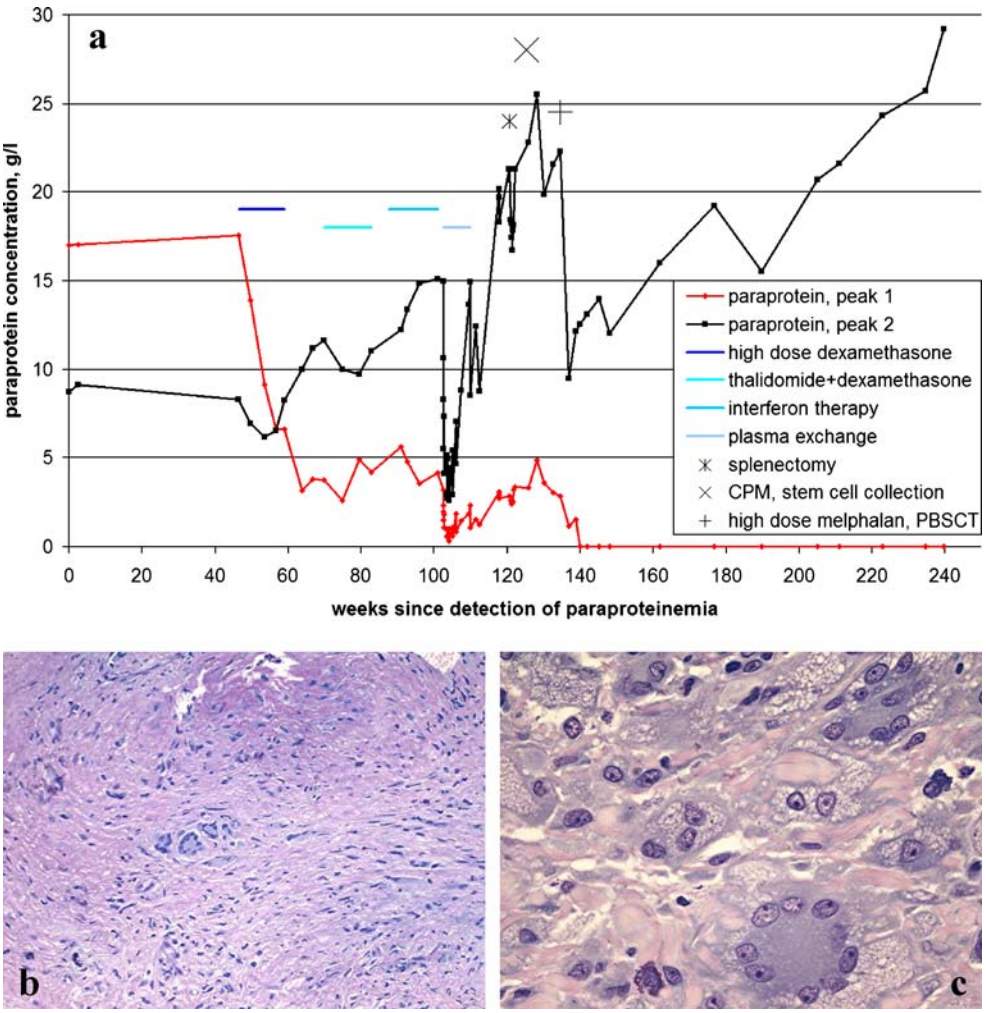

Fig. 1 **a** Summary of treatment and evolution of paraprotein concentration: Time points for splenectomy, cyclophosphamide (*CPM*) treatment with stem cell collection and peripheral blood stem cell transplantation (*PBSCT*) are indicated. **b** Histological specimen of the right upper eye lid: low power view showing hyaline material and a few giant cells. **c**: High power view with foam cells, giant cells with two and three nuclei and a multinucleated Touton type giant cell

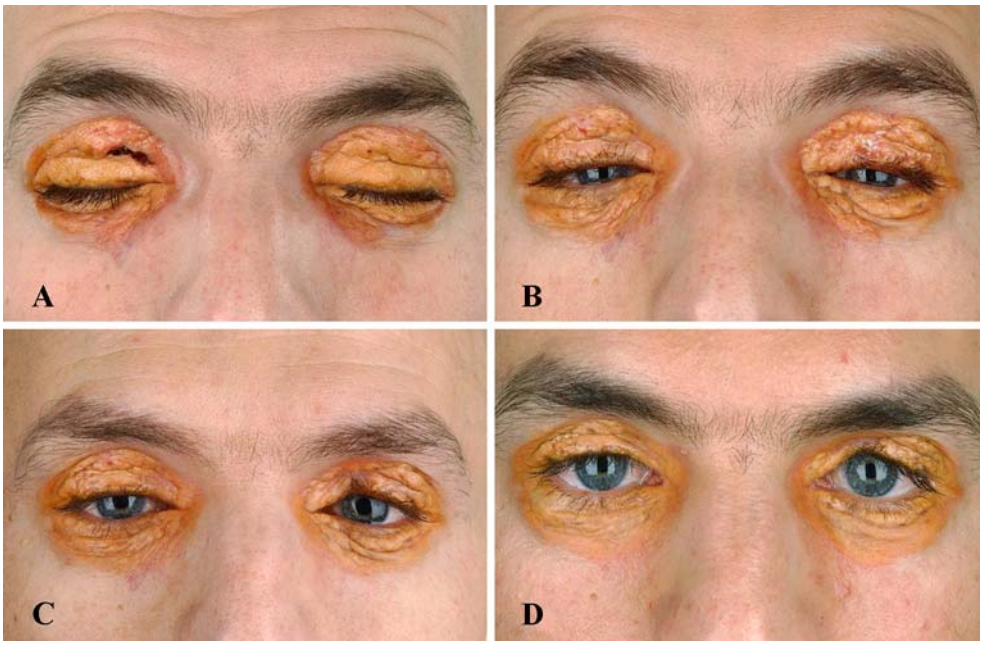

Fig. 2 Facial aspect of our patient. **a** November 2003: Indurated palpebral and periorbital infiltrates. The palpebral fissure was severely narrowed, causing mechanical blindness. **b** April 2004: After splenectomy, the infiltrates had softened, accompanied by improvement of vision. **c** June 2004: Further clinical improvement 2 weeks after autologous stem cell transplantation. **d** September 2004: Three months after transplantation, the patient had regained vision

cells; however, repeated microscopic examinations of bone marrow aspirates were normal with no signs of myeloma. After splenectomy, the peripheral blood count nearly normalized. Interestingly, a transient improvement of paraproteinemia and eye infiltrates was also noted (Figs. 1a and 2b). Because of the severity of the disability, we decided to proceed to high-dose chemotherapy with PBSCT. Stem cells were collected using cyclophosphamide mobilization. The patient was conditioned with melphalan (200 mg/m^2) and dexamethasone in June 2004. A second PBSCT was declined by the patient. A few weeks after the PBSCT, the eye infiltrates started to improve (Fig. 2c,d). Cosmetic and functional recovery was achieved within the next 6 months. At the time of writing, 26 months after transplantation, the patient remains free of symptoms (Fig. 3). Paraprotein concentration had temporarily improved; however, within the last 14 months, a continuous increase above the level before transplantation has been observed (Fig. 1a).

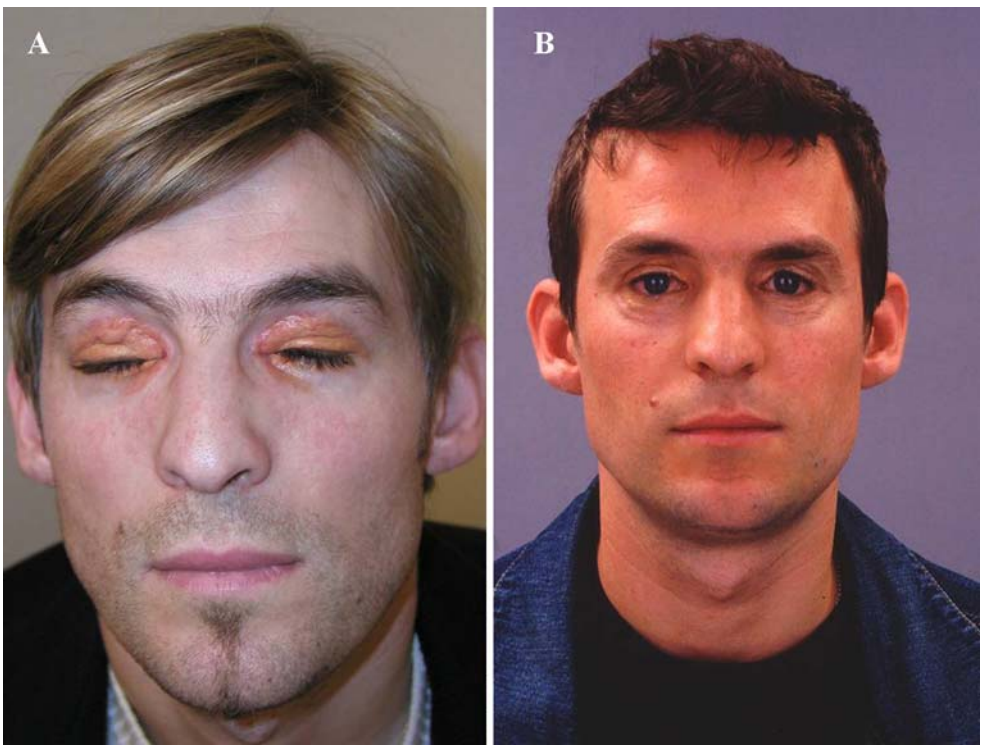

Fig. 3 Facial aspect of our patient. **a** In 2002, before treatment. **b** In 2006, 12 months after autologous stem cell transplantation. The patient is now free of symptoms

Discussion

NXG is a rare complication of paraproteinemia. The chain of events leading to skin infiltrates in NXG is not understood. It has been suggested that the paraprotein binds to lipoproteins. These complexes would be deposited in the dermis and taken up by histiocytes, leading to foam cells and a foreign body giant cell reaction [3, 9]. According to another hypothesis, the paraprotein would directly bind to macrophages inducing activation and inflammation [10, 11]. No biochemical evidence for either hypothesis has been presented. In about 20% of all cases, no monoclonal protein is detectable [1, 2], suggesting that non-neoplastic antibodies can also trigger the dermal inflammatory reaction. Without treatment, the skin infiltrates usually progress; spontaneous remissions are rare. Survival rates between 45 and 95% have been reported after 10–15 years of follow-up. Most non-survivors had died of multiple myeloma or apparently non-related neoplasms. The best therapeutic results have been achieved with strategies directed against the paraprotein or the neoplastic B-cell clone producing it. The options reported include high-dose dexamethasone, anti-myeloma chemotherapy, plasmapheresis and interferon-α. As in our patient, usually incomplete or transient relief is achieved by these therapies. Surgery is considered contra-indicated because ineffective wound healing can worsen the condition [3]. However, in a recent report, improvement of palpebral infiltrates was achieved by skin grafting from a non-affected region [12]. In our patient, PBSCT provided a long-lasting remission. To our knowledge, this is the first report of PBSCT in a patient with NXG. Interestingly, in our case, initially two peaks of an IgGκ paraprotein were detected. During the course of the disease, changes of peak 1 (closest to the β-globulins) correlated strongest with palpebral infiltrates. After PBSCT, peak 1 had disappeared, progression of peak 2 was not accompanied by ophthalmologic complaints (Fig. 1a), suggesting that these two IgGκ peaks are actually separate clones rather than monomers and aggregates of M protein of one clone. It is tempting to speculate that, in our patient, only peak 1 caused NXG, whereas the more therapy-resistant peak 2 is not associated with skin infiltrates. Interestingly, although having pronounced symptoms of NXG, the cholesterol level of our patients was very low (1.9 mmol/l in May 2004), possibly indicating an anti-lipid activity of the paraprotein. After successful treatment, cholesterol levels normalized (4.5 mmol/l in August 2006). In summary, in our patient, autologous stem cell transplantation has been a safe and effective therapy for NXG. Our data broaden the therapeutic options for patients suffering from this rare condition and provide further evidence for a crucial role of the paraprotein in the pathogenesis of this disease.

References

1. Kossard S, Winkelmann RK (1980) Necrobiotic xanthogranuloma with paraproteinemia. J Am Acad Dermatol 3(3):257–270
2. Mehregan DA, Winkelmann RK, Wilson Jones E (1992) Necrobiotic xanthogranuloma. Arch Dermatol 128(1):94–100
3. Ugurlu S, Bartley GB, Gibson LE (2000) Necrobiotic xanthogranuloma: long-term outcome of ocular and systemic involvement. Am J Ophthalmol 129(5):651–657
4. Chave TA, Chowdhury MM, Holt PJ (2002) Recalcitrant necrobiotic xanthogranuloma responding to pulsed high-dose oral dexamethasone plus maintenance therapy with oral prednisone. Br J Dermatol 144(1):158–161
5. Criado PR, Vasconcellos C, Pegas JR, Lopes LF, Ramos CF, Tebcherani AJ et al (2002) Necrobiotic xanthogranuloma with lambda paraproteinemia: case report of successful treatment with melphalan and prednisone. J Derm Treat 13(2):87–89
6. Georgiou S, Monastirli A, Kapranos N, Pasmatzi E, Sakkis T, Tsambaos D (1999) Interferon alpha-2a monotherapy for necrobiotic xanthogranuloma. Acta Derm Venereol 79(6):484–485
7. Finelli LG, Ratz JL (1987) Plasmapheresis, a treatment modality for necrobiotic xanthogranuloma. J Am Acad Dermatol 17 (2):351–354
8. Schaffner A, Augustiny N, Otto RC, Fehr J (1985) The hypersplenic spleen. A contractile reservoir of granulocytes and platelets. Arch Intern Med 145(4):651–654
9. Bullock JD, Bartley GB, Campbell RJ, Yanes B, Connelly PJ, Funkhouser JW (1986) Necrobiotic xanthogranuloma with paraproteinemia: case report and a pathogenetic theory. Ophthalmology 93(9):1233–1236
10. Rappersberger K, Wrba F, Heinz R, Zonzits E, Hönigsmann H (1989) Necrobiotic xanthogranuloma in paraproteinemia. Hautarzt 40(6):358–363
11. Char DH, LeBoit PE, Ljung BM, Wara W (1987) Radiation therapy for ocular necrobiotic xanthogranuloma. Arch Ophthalmol 105(2):174–175
12. Schaudig U, Al-Samir K (2004) Upper and lower eyelid reconstruction for severe disfiguring necrobiotic xanthogranuloma. Orbit 23(1):65–76