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Use of imatinib in a patient with cutaneous vasculopathy in the context of von Recklinghausen disease/ neurofibromatosis

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Summary

von Recklinghausen disease/neurofibromatosis (NF) is caused by an autosomal dominant mutation in NF1, resulting in a deficiency of neurofibromin 1, a protein with a tumour suppressor function in the Ras–extracellular regulated kinase pathway. The disease comprises a variety of clinical manifestations, including vascular abnormalities. Large vessel abnormalities are well known, while small vessels of the skin are very rarely involved. The latter can cause livedo, necrosis and painful ulcers. For such ulcers, all invasive therapies (e.g. surgery and radiotherapy) are harmful and should be avoided. Herein, we describe a patient with NF and cutaneous vasculopathy treated with imatinib, a tyrosine kinase inhibitor.

What's already known about this topic?

- Vascular abnormalities in neurofibromatosis (NF) are well described but cutaneous vasculopathy is not.

What does this study add?

- This is the third description of a patient with cutaneous vasculopathy.
- We report the first patient to receive imatinib in this indication.
- A better knowledge of the physiopathology of vasculopathy in NF can allow us to think about new therapies.

Neurofibromatosis (NF), also known as von Recklinghausen disease, is caused by an autosomal dominant mutation in NF1, resulting in a deficiency of neurofibromin 1, a protein with tumour suppressing activity in the Ras–extracellular regulated kinase (ERK) pathway.[1] It is an autosomal dominant disorder with a variable penetrance.

The clinical picture is varied. Typical signs of NF include neurofibromas, multiple café-au-lait macules, axillary and inguinal freckling, and iris hamartomas (Lisch nodules). The first description of vascular lesions in NF was made in 1945.[2] Since then, cerebral and peripheral vasculopathy have been well described in the literature, while cutaneous vasculopathy is rare and very little is known about it.

Case report

A 42-year-old woman, who had NF since she was 8 years old, with slight cognitive impairment, multiple café-au-lait macules, axillary and inguinal freckling, Lisch nodules and numerous small and giant plexiform neurofibromas was hospitalized in January 2008 when a livedo and necrotic plaques appeared on both her thighs (more significantly on the right one), strictly limited to the site of two giant plexiform neurofibromas. Deep and painful ulcerations developed rapidly and, on admission, a clinical diagnosis of occlusive vasculopathy was made (Fig. 1). Sedimentation rate, C-reactive protein, extensive coagulation tests (bleeding time, partial thromboplastin time, platelet

Fig 1. A necrotic, livedoid and painful ulceration of the thigh.

aggregation test, prothrombin time, protein C and S determination), complete blood count, antiphospholipid antibodies, cryoglobulins and cryofibrinogen were normal. In addition, no monoclonal immunoglobulin was detected. There was no evidence of cholesterol emboli.

Deep venous thrombosis and arterial occlusion of the right leg was ruled out by Doppler sonography, a normal ankle brachial index and transcutaneous oximetry. Furthermore, computed tomography angiography showed normal arteries of large calibre, with the exception of a giant aneurysm of the left internal carotid artery that was 22 mm in diameter. Phlebography showed a patent greater saphenous vein and collateral venous network, possibly due to a thrombosis or compression of the saphenous vein (Fig. 2). Magnetic resonance angiography of the patient's right thigh showed cutaneous necrosis down to the subcutaneous fat, in contact with the greater saphenous vein. The latter was dilated with a very irregular diameter and small expansions along its course, suggestive of a varicose vein. Magnetic resonance imaging of the patient's right thigh showed several neurofibromas along the sciatic and femoral nerves, with the biggest measuring 5 cm.

Fig 2. Phlebography showing a patent greater saphenous vein and collateral venous network.

Numerous biopsies of lesional skin were performed to further characterize the vascular changes. Proliferating, randomly arranged spindle-shaped cells with elongated wavy nuclei in the mid- and deep dermis were noted, representing the plexiform neurofibroma. Multiple vessels of varying calibre, positive for CD31 and CD34, but negative for the D2-40 lymphatic vessel marker, were present in the deep dermis and subcutis. Elastic laminae were absent in van Gieson elastin stainings. Moreover, there were large vessels with thickened walls and proliferating myofibroblasts expressing α-smooth muscle actin. We also found smaller and partially thrombotic vessels. Vessels were surrounded concentrically by proliferating epithelial membrane antigen-positive cells, as well as S-100 neural proliferating cells (Fig. 3a,b). Skin biopsies of clinically normal skin showed no vascular abnormalities.

Taken together, the information obtained from the radiological investigations and the biopsies allowed us to conclude that the patient had large vessel disease, as well as cutaneous vessel abnormalities consisting of intimal proliferation, stenosis and thrombosis in the dermis and subcutis, which led to the clinical picture of livedo, necrosis and subsequent ulcerations. Because of the presence of the livedo, we thought at first that the problem was the vasoconstriction of vessels, which is why we initially administered antithrombotic medication (aspirin, coumarin derivatives and heparin), vasodilators (calcium channel blockers, α-1A antagonist tamsulosin and prostacyclins) and β-blockers (propranolol). Then we tried to treat the patient as if she had a proliferating disease, and administered topical and systemic corticosteroids, interferon-α 2A and sirolimus, all of which were used unsuccessfully. Excision and autologous skin grafting of the necrotic ulcer led to extensive new necrotic lesions.

As the lesions progressed throughout the year, we initiated therapy with imatinib after obtaining the patient's consent. This approach was based on findings by Lasater *et al.*,[3] linking a deficiency of neurofibromin with hyperactivation of the Ras–ERK pathway. Hyperactivation of this pathway leads to myofibroblast proliferation in injured rat vessels, which can be prevented by imatinib, a tyrosine kinase inhibitor. As we observed myofibroblast proliferation and vessel stenosis in our patient, this approach seemed promising.

Imatinib was administered at a dose of 400 mg daily for 2 years. It was well tolerated from a haematological point of view but the severe abdominal pain and vomiting experienced by the patient forced us to abandon the treatment after a reduction in dose to 200 mg daily did not alleviate the side-effects. By the end of the treatment, during the winter of 2011, it appeared that wound healing was well underway (Fig. 4). Since discontinuation of imatinib, the patient's ulcers have been expanding and contracting. Complete healing has

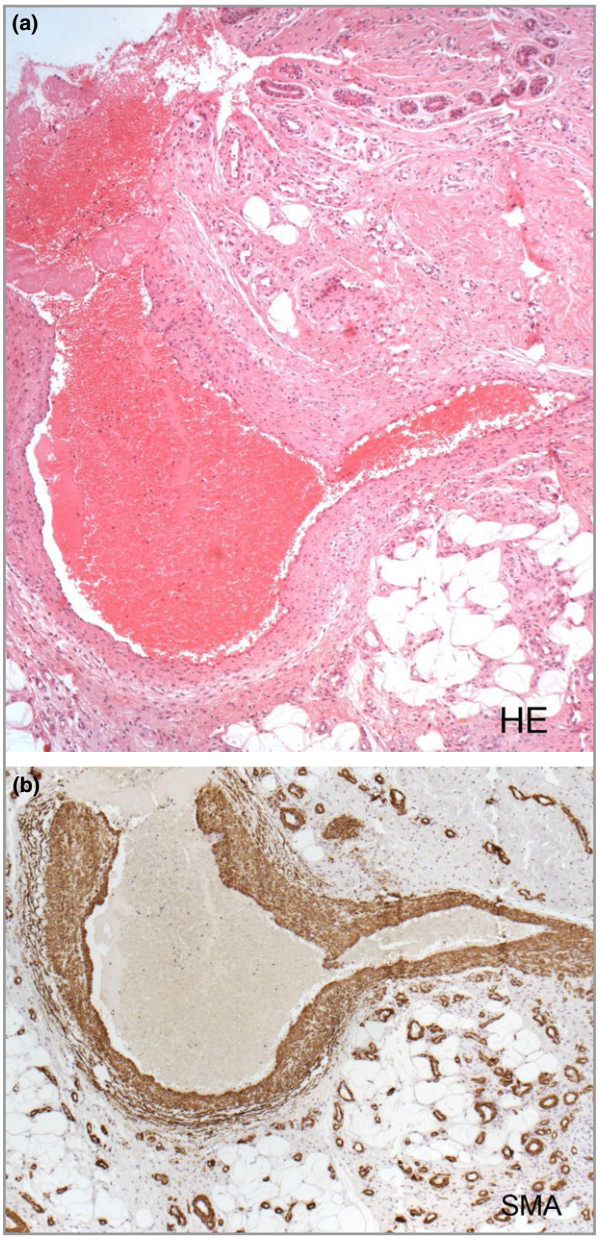

Fig 3. (a, b) Neurofibromatosis. Large vessels with thickened walls and proliferating myofibroblastic cells, expressing α-smooth muscle actin (SMA). HE, haematoxylin and eosin.

not been achieved. With imatinib treatment, the necrotic ulcer became linear and almost healed. At its worst, the ulcer was burrowing and 20 × 15 cm in size. The result obtained while receiving imatinib was not obtained before or after treatment with this medication.

Radiotherapy applied recently to part of the lesion resulted in a large and painful ulceration, thus confirming our previous fears of vessel occlusion being initiated by injury.

Discussion

Vascular abnormalities in NF are well described in both the paediatric and adult literature. NF vasculopathy comprises

Fig 4. Neurofibromatosis. Accelerated closure of the ulcer with imatinib treatment.

arterial stenosis, occlusion, aneurysm, pseudoaneurysm, rupture or arteriovenous fistula formation. For some authors, the vasculopathy is thought to be of prenatal onset.[4] According to large clinical series, both cerebral and peripheral vasculopathy in adults have a prevalence ranging from 0·4% to 6·4%.[5] The incidence of vascular pathology is probably underestimated, as most of the vascular features are asymptomatic.[6] However, major cardiac and cerebral vessel involvement can have life-threatening consequences.[7,8]

Cutaneous vasculopathy in NF is extremely rare. To our knowledge, it has been reported only twice.[9,10] Neurofibromin, the deficient protein in NF, plays an important role in growth control and differentiation of cells. In its absence, endothelial and smooth muscle cells proliferate, and the resulting vessels show different abnormalities, notably (i) increased fragility of vascular walls causing aneurysms; (ii) stenosis and occlusion; and (iii) arterial ruptures causing arteriovenous fistulas.

The genetic deficiency is not the only factor. It is proven that the vascular abnormalities in patients with NF increase with age. Thus, environmental factors (e.g. injury, smoking, exercise, stress) may play a role in stimulating intimal proliferation via the Ras–ERK pathway leading to stenosis and occlusion of vessels.[3,11] In our patient, every surgical aggression or trauma gave rise to new bouts of necrosis and ulceration.

Several authors have demonstrated that inhibition of the platelet-derived growth factor (PDGF)-BB Ras–ERK pathway prevents neointimal proliferation after arterial injury in NF mice. Lasater *et al.*[3] went on to demonstrate that NF1 mice, pretreated with imatinib mesylate, did not develop vascular smooth muscle proliferation or arterial stenosis after vessel injury. Imatinib mesylate (Gleevec®; Novartis, East Hanover, NJ, U.S.A.), initially used in chronic myeloid leukaemia, is a selective inhibitor of the BCR/ABL tyrosine kinase that blocks the activation of the Ras–ERK pathway via PDGF receptor (PDGFR) and thus the intimal proliferation.

To our knowledge, the patient reported herein is the first to receive imatinib mesylate in NF vasculopathy. The treatment

can be regarded as partially successful as we obtained the best result achieved thus far with regard to wound closure, although complete healing was not achieved.

The lack of complete healing might be explained by the inevitable repeated minor traumas experienced by the patient during daily life, an insufficient plasma level of imatinib (NF mice received a 10-fold higher dose of imatinib than our patient) and the fact that we had to abandon treatment because of the major digestive side-effects experienced by the patient. With regard to the only two other patients with skin vasculopathy published to date, all medications used – prednisolone, ciclosporin, mycofenolate mofetil and dapsone,[9] and steroids, cyclophosphamide bolus therapy and infliximab, respectively[10] – were unsuccessful and brought no improvement.

Imatinib in $NF1^{+}$ mice has been shown to reduce the size of neurofibromas.[12] Of note, we did not observe any reduction in the size of the patient's neurofibromas.

Recently, an open-label phase 2 trial, based on these results, has also demonstrated a reduction in volume of clinically significant plexiform neurofibromas in patients with NF.[13] Sorafenib, another inhibitor of tyrosine protein kinases (vascular endothelial growth factor and PDGFR) and Raf kinases, is being tested for this indication.[14,15]

In summary, cutaneous vasculopathy is extremely rare in patients with NF. According to our understanding of the physiopathological mechanisms, new tyrosine kinase inhibitors with fewer side-effects may be useful in preventing intimal proliferation. Aggressive surgical treatments should be avoided at all costs.

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