

Cell Therapy in Angiopathies and Their Consequences (Ulcers, Phlegmons, Gangrenosis)

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The chronic obliterative angiopathy of the arteries of the extremities, generally called peripheral arterial occlusive disease (PAOD), associated with a generalized arteriosclerosis and its consequences, such as ulcers, gangrenosis, soft-tissue and bone infections are still an unsolved therapeutical problem. In our latitudes about 6% of the population is affected by it.

Etiology of the peripheral arterial occlusive disease is multifactorial, its manifestation is uni- or multilocular. Similar clinical pictures are caused by different causes. Numerous diseases (heart, circulation, lung, blood diseases, kidney, liver, nervous system, gastroenteropathies, rheumatic diseases and disorders of the immune system) can play a part in it.

The risk factors are very important as well. Those are, above all, diabetes and other metabolic diseases, such as hypercholesterolaemia, hypertriglyceridaemia, hyperuricemia, smoking, hypertension, stress, haemorrheologic causes, respiratory insufficiency, lack of iron, disorders of the water balance, lack of exercise, malnutrition, inadequate habits.

The risk of developing an obliterative angiopathy is extremely high in patients with two or more risk factors. The FONTAINE'S classification distinguishes 4 stages:

1. Lack of symptoms or paresthesia in one extremity
2. Intermittent claudication
3. Rest pain, maybe trophic disorders in the initial stages
4. Ulcer and gangrene

In most cases symptoms only start when there is a 75% stenosis of the arteries, in diabetics frequently only with a 90% stenosis. In diabetics you will almost always find a neuropathy of the lower extremities, which may cause a state of complete numbness, as well. Thus these patients frequently are not aware of the severe changes taking place in their feet. If, in addition, there is a diabetic retinopathy, the patients cannot see their ulcers or gangrenosis either. Consequently they only start medical treatment when marked changes, such as gangrenes or or pedal phlegmons have already developed.

In my function as orthopaedic consultant physician of the hospital *Rudolfstiftung* (Rudolf Foundation) in Vienna (Austria), which has a capacity of 838 beds, I am quite often confronted with the consequences of vascular occlusions. Ulcers, gangrenosis, phlegmons, osteolyses, osteomyelitis, patients' conditions following vascular operations and amputations with defective wound healing requiring orthopaedic treatment. Quite often the decision has to be made whether, when and at which point the amputation should be performed.

For more than 7 years I was rather helpless as regards these clinical pictures. In 1982 I introduced cell therapy within the orthopaedic outpatient department. The main cell

types applied were "Resistocell" and placenta. Treatment results have improved considerably since then.

Vascular operations combined with cell therapy definitely require close cooperation with the vascular surgeon and the internist. The majority of the vascular operations were carried out by the senior surgeon Michael Müller of the 2. Department of Surgery of the *Rudolfstiftung*.

If an operation is inevitable, cell therapy may be applied pre- or postoperatively. If there is enough time, that is if you can wait for the effects of the cells to set in, wound healing in most cases will be better. In some cases it is possible to carry out an amputation further distally, that means that it is enough to amputate the fore- or midfoot, instead of carrying out a below-knee amputation.

It is possible to modify the amputation technique after the the cellular effects set in: You simply amputate at the limit between necrotic and healthy tissue and leave the wound open, or simply put in retention sutures or apply loose adhesive strips. Thanks to the improved blood circulation, which makes itself apparent in the improvement of the microcirculation, and the complex cellular effects which improve metabolism, even in apparently hopeless cases a complete wound healing can be achieved. If the amputation is unsuccessful, cell therapy creates a better condition for an ablation further proximal, which means that a stump remains to which an orthopaedic shoe or prothesis can be attached. Prognosis is bad, because there are almost always coronary and cerebral sclerosis. 41% of the patients do not live longer than 5 years.

Pedal phlegmons

Pedal phlegmons are frequent in diabetics with occlusive disease and neuropathy. Infections usually are caused by small ulcers of the toes, paronychia, infected plantar clavi and eczematous and fungal diseases of the cutis. Apart from diseases of the soft-tissue, quite often there are alterations of the bones, which may reach from macular osteoporosis to destruction of the bones with complete osteolysis. This happens usually in the area of the metatarsal bone (CHARCOT foot).

Pedal phlegmons, in most cases, are treated with antibiotics, surgical incisions and counterincisions with drainage. If it is not necessary to amputate previously it normally takes months or years for pedal phlegmons to heal up. It is possible to considerably reduce the duration of the healing by administering cells pre- or postoperatively.

Ulcers

Ulcers in legs or feet, caused by arterial occlusion or venous diseases, can be mostly cured by administering cells. This is also true for stump ulcers following amputations or vascular operations. In such cases it is important to perform a consistent wound toilet, this means to continuously necrectomize the remaining necrotic tissue, freshen up the cutaneous borders of the ulcer, apply enzymatic ointments and give wound-cleaning tepid baths with camomile, betaisodona or H_2O_2 .

Case Reports

Case 1

In February 1984 the 73-year-old diabetic S.H. came to the orthopaedic out-patient department suffering from a chronic diabetic angiopathy of the lower extremities. Inoperable multiple vascular occlusions were diagnosed. The fourth and fifth toe had been amputated months ago, due to gangrenosis. The wound around the fifth toe had not shown any tendency to heal. An X-ray showed lysis of the head of the metatarsal bone V. Its rests were removed and placenta and "Resistocell" were implanted. 5 months later the wound had completely healed up. Only 2 years later did a pregangrenous state in the area of the third toe on the left recur.

Case 2

In February 1986 the 42-year-old patient Sch.J. was referred from the Department of Dermatology for orthopaedic treatment. He suffered from a chronic obliterative angiopathy and neuropathy of the left lower extremity caused by nicotine and alcohol abuse. A large medial ulcer was diagnosed in the left foot, reaching from the navicular bone to the second toe. The hallux and the first metatarsal bone had already been amputated 2 years earlier, due to gangrenosis. Implantation of "Resistocell" in February and April 1986. 6 months later the defect had healed completely.

Case 3

The 67-year-old female patient L.A. suffered from latent diabetes with angiopathy. In November 1984 a bone operation (removal of the cuneiform of the heel bone according to DWYER) was carried out because of a pes planovalgus and a marked artrosis of the tarsal bone. Chronic osteomyelitis and phlegmons of the right foot developed. Various antibiotic therapies and immobilization did not achieve healing. The patient was simply discharged after months without having been healed.

When therapy was initiated the partially fixed splay foot was extremely swollen and had turned livid. There was a plantar wound, 10 cm long, with a hyperkeratotic border. At the plantar side of the heel bone there was a fistula which had gone through into the bone. The erythrocyte sedimentation rate was 76/110, leucocytes 11,000. Due to severe pain the patient was unable to put any weight on the foot.

In May 1985 placenta and "Resistocell" were implanted. First the fistula healed up and then the wound diminished progressively. Continuous necrectomy and resection of the borderline hyperkeratosis. 2 months later repetition of "Resistocell" administration. The wound continued to get smaller, the swelling disappeared and mobility improved. In April 1986, 11 months after initiating the treatment, a further implantation of "Resistocell" and placenta was carried out. In October 1986 - 17 months after starting the treatment - the wound had closed and the patient was able to walk well with orthopaedic shoes. The erythro-sedimentation had dropped to 18/32, leucocytes to 6,800.

Case 4

In May 1985 the 64-year-old female patient S.H. was referred to the Orthopaedical Department because of diabetic gangrenes in every toe.

Diagnosis: Dry gangrene in every toe associated with peripheral vascular occlusion with multiple stenoses in the area of the right lower extremity. A vascular operation was not possible.

Administration of "Resistocell". 2 weeks later semicircular amputation of the forefoot, proximal of the metatarsal heads. Development of necroses at borders of wound and excision of those. Subsequently continuous necrectomies and treatment with baths and enzymatic ointments. In November 1987, after 6 months of treatment, the wound had healed up. The patient is able to walk comfortably with orthopaedic shoes.

Case 5

The 73-year-old female diabetic W.J. started orthopaedic treatment at the beginning of 1986. In 1985 a below-knee amputation on the right had been carried out after a vascular occlusion and an unsuccessful operation. On the left plantar side above the heel bone, an ulcer about 10 cm in diameter with an exposed bone was diagnosed. This was the condition following a femorocrural bypass. In January 1986 "Resistocell" was administered, followed by necrectomy of the necrotic tissue at the border of the ulcer as well as a consistent wound toilet, as described above. 11 months later the ulcer had closed up. In most cases ulcers in the area of the plantar heel cannot be cured with conventional methods and lead to a below-knee amputation.

Case 6

The 62-year-old patient M.F. suffered from a type II diabetes. A plantar ulcer in the area of the left heel and multiple, inoperable vascular occlusions were diagnosed, as well. The bone was fully exposed. In October 1986 administration of "Resistocell". Healing was slow. 6 months later reimplantation of "Resistocell". In September 1987, that is 11 months later, the ulcus had closed.

Case 7

The patient R.H. had been suffering from insulin deficiency diabetes since he was 10 years old. He was 45 years old when admitted to the 2. Medical Department of the *Rudolfstiftung* (Prof. SLANY) for treatment of a pregangrenous state in the second toe on the right, associated with chronic obliterative angiopathy. In 1984 after years of dialysis a kidney transplantation was carried out successfully. In 1985 occlusion of the femoral artery and the popliteal artery on the left hand side. Below-knee amputation on the left. It seems that a vascular operation had not been carried out because of the kidney transplantation.

The second toe on the right is dark purple and presents a lense-size necrotic skin area, dorsally above the middle

and distal phalanx. Although vasodilative infusions maintain constant the condition of the toe there is no improvement. The oscillogram is completely negative, in the photoplethysmography of the first and second toe no activity is to be seen. 3 weeks after administration of cells the previously cold lower leg starts to warm up progressively, in a distal direction, warming 10 cm per week, until the toes are warm. The second toe starts to become pink, the skin necrosis heals up. The plethysmography of the first and second toe, 3 months after cell implantation, shows high oscillations. 5 1/2 months later the toes start cooling again, repetition of "Resistocell" and liver implantation. This implantation, like the first one, is tolerated without any complications. The leg and the foot again get noticeably warmer.

Case 8

The 70-year-old female patient M.A. who has been suffering from insulin deficiency diabetes for 20 years is admitted to the 2. Medical Department of the *Rudolfstiftung* in February 1987. Diagnosis: Gangrene of the forefoot and the midfoot, occlusion of the superficial femoral artery, blood sugar 311 mg %.

Implantation of "Resistocell". Due to the progression of the gangrene it is not possible to wait for more than 4 days. Carrying out of a femorocrural bypass with the help of the resected great saphenous vein. 3 days later atypical CHOPART'S mediotarsal amputation. It is hard to get the skin to close. In consequence the skin and the subcutis become necrotic which means that the operation has been a failure.

In this case vascular operation and cell therapy came late. These measures, naturally can only be successful if the ischaemic damage of the tissue in the area of the amputation site is not too severe. If there are no or very few revitalizable cells or structures, even cell therapy - especially if there is not enough time - cannot show any effects.

Case 9

The 72-year-old patient L.F. is admitted to the 2. Surgical Department of the *Rudolfstiftung* (Counsellor medical superintendent Dr. Huber) on October 22nd, 1985. Diagnosis: Pedal phlegmons, occlusion of the superficial femoral artery associated with diabetes and nicotine abuse. On October 23rd, 1986 incision of the plantar phlegmons and necrectomy. Necrotic material of the size of a chicken egg is removed. 2 weeks later administration of "Resistocell" and discharge of the patient. The wound is granulating, but shows only a very limited healing tendency. In January 1987, 1.5 months later, after renewed administration of "Resistocell" a femoropopliteal bypass using the great saphenous vein is carried out. Subsequently, whilst performing continuous wound toilet, granulations are clearly to be seen and after 7 months the ulcer has completely healed up. The patient receives cell implantation at 1 year intervals, since the ulcer repeatedly threatens to rupture again.

Case 10

In June 1982 a 39-year-old, extremely obese patient with type I diabetes is admitted to the 2. Surgical Department of the *Rudolfstiftung*. Diagnose: Phlegmons of the foot and the lower leg with gangrenes in every toe. The foot, lower and upper leg are extremely swollen and have turned livid, the toes are black. Erythrocyte sedimentation rate 109/111, leucocytes 15,900, blood sugar 299 mg %. Deep leg vein thrombosis in the anamnesis.

I was consulted by the Department to help determine the point of amputation. Of 5 specialists in surgery 3 opted for a below-knee amputation and 2 even for an above-knee amputation. It took me all my powers of persuasion to convince them to give cell therapy a try. For the time being a provisional amputation at the border of the wet gangrene of the toes was carried out, proximal of the metatarsal heads. Cell administration of "Resistocell" and placenta. Already 2 weeks later the extremity looks better and sloughing of the necrotic tissue at the amputation site starts. Granulation tissue becomes apparent. One week later a reamputation in the area of the base of the metatarsal bones is carried out. A whole cuff of necrotic cutaneous and soft-tissue material is excised and the soft parts are simply loosely sewn together with some retention sutures. 5 weeks after implantation the patient leaves the hospital with a thumb-nail-sized residual ulcer. He is given an orthopaedic shoe and 6 weeks later he is able to work normally as the boss of an electrical company.

Case 11

In January 1986 the 76-year-old female diabetic K.A. is admitted to the 2. Surgical Department. There is an acute ischaemia of the right lower leg and the foot. The angiography shows a short occlusion of the popliteal artery.

On January 30th, 1986 a femorocrural bypass is carried out. Afterwards the foot pulse is easily palpable. Nevertheless a necrosis of almost all the lower-leg musculature, except the triceps surae, develops. 4 days after "Resistocell" implantation a radical resection of the necrotic musculature sparing the vessels and nerves was carried out. In consequence there is an extended wound reaching from the distal part of the lower leg to the middle part of the upper leg. Due to resection of all the dorsiflexor muscles and the peroneal musculature there is a complete dangle foot. Already 1 week after administration of cells distinct granulation is observed. Again, consistent wound toilet is performed. Mobilization of the patient with a functional peroneal splint. The wound granulates continuously and 3 months later the patient is discharged with a residual wound in the area of the knee joint. 4 weeks later, this is 4 months after the operation and the cell administration, the wound is completely closed.

Case 12

The 74-year-old female patient H.T. suffers from digital and forefoot gangrenes and various ulcers on the exterior

side of the left lower leg. The angiogram shows an occlusion of the deep femoral artery due to arteriosclerosis.

On March 26th, 1985 a deep femoral artery plastic operation is carried out with the help of a venous patch, in order to - as the surgeon writes in the operation report - at least make a lower-leg amputation possible. 4 days later administration of "Resistocell". 14 days later semicircular forefoot amputation at the border between the middle and proximal third of the metatarsal bone. On the plantar side there is a large cutaneous flap left, which is well supplied with blood. It is turned in dorsal direction and sewn medially with the skin at the back of the foot. Since it is laterally too short it is being simply "stitched onto" the ulcer situated there. This procedure, contradicting every rule of limb surgery, is however very successful. In conventional medicine such a case compulsorily indicates a lower-leg amputation.

After 4 weeks of consistent wound toilet the ulcers on the lower leg were the first to close. 4 months later the lateral ulcer at the dorsum of the foot was almost completely closed. The patient is discharged and receives outpatient treatment. 4 weeks later the ulcer has healed up and the patient is more or less able to walk with an orthopaedic shoe.

Summary

In patients with PAOD in stages I and II physical means of treatment are applied, above all training in walking. Here cell therapy can be applied very successfully. Increase in circulation is measurable subjectively as well as objectively.

In stages III and IV the operative reconstruction of the occluded part of the vessel or the recanalization by catheters or systemic lysis are most important (streptokinase, prostaglandin). As mentioned above it is also possible to carry out pre- or postoperative organotherapy. In more than 2/3 of all patients, especially in diabetics with multiple stenoses, an operation is not possible any more. Apart from the usual conventional measures, cell therapy can be very helpful here. Care is required in using the so-called vasodilative agents. The so-called steal effect, this is an enhanced blood flow in the cutaneous vascula or intact muscular vessels, can cause a further reduction of the blood flow in the damaged tissue.

Many books recommend to keep necroses and gangrenosis absolutely dry, so that no wet gangrene can develop. However when carrying out pretreatment with cells we do exactly the opposite. After the effects of the cells have set in we treat the necroses operatively and carry out necrectomies which leads to the development of ulcers which are then induced to heal by administering incarnative agents. Gangrenosis of the toes or of the foot require amputation. In the ideal case about 3-4 weeks after cell administration the primary healing of amputation wounds is very frequent. In healing by secondary intention consistent

wound toilet has to be observed which entails the meticulous necrectomy of necrotic tissue - a tedious task requiring a lot of patience and one that is hardly ever tolerated by patients not having neuropathy without anaesthesia.

Final observations

Between 1982 and 1987 a total of 191 patients with consequences after PAOD were treated in the hospital *Rudolfstiftung*. The main cell types were "Resistocell", and as per the individual requirements, sometimes placenta too. It was possible to cure or considerably improve the condition of 114 patients, which are 69%. Here you have to bear in mind that part of this patient group were hopeless cases with infaust prognosis.

NIHEANS' therapy, when applied alongside with the therapeutical methods of conventional medicine, can considerably improve blood flow in peripheral arterial occlusive disease. Ulcers, soft-tissue and bone diseases can frequently be healed, even in, apparently hopeless cases. Healing by first or second intention of amputation stumps can be improved considerably by adminisitering cells. Last but not least, in some cases it is even possible to move the point of amputation further distally. Organotherapy and therapeutic methods of conventional medicine should be combined and applied globally and sensibly. They should not compete with one another - with an optimal combination the effects can not only add up but, in the ideal case, even potentiate.

After the incomprehensible prohibition of cell therapy in 1987, treatment of the consequences of PAOD at the orthopaedic outpatient department of the *Rudolfstiftung* has returned to the original state. Phlegmons, ulcers and gangrenosis are treated conservatively and amputation height forefoot, midfoot or lower leg is determined. Many patients, who had been receiving cell therapy at 6 to 12 month intervals had to undergo an amputation or reamputation - and the cell therapist has been forced to helplessly watch this happen.