Healing of Skin Necrosis and Regression of Anticardiolipin Antibodies Achieved by Parathyroidectomy in a Dialyzed Woman with Calcific Uremic Arteriolopathy

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Aim. To present the impact of parathyroidectomy on the spontaneous healing of necrotic lesions of the skin of the lower leg and on anticardiolipin antibodies regression in a 68-year-old female dialyzed patient with hyperparathyroidism and calcific-uremic arteriolopathy (CUA).

Methods. After the occurrence of initial lesions of the lower leg skin, the intact parathyroid (iPTH) level, calcium (Ca) and phosphorus (P) product were measured, and on two occasions at 6-week intervals, the titer of anticardiolipin antibodies was determined, followed by a clinical monitoring of the progress of necrotic skin lesions. Two months after the occurrence of the skin lesions, the patient's right leg was amputated below the knee due to gangrene, and a histopathological analysis of the skin tissue sample of the amputated lower leg was made. After parathyroidectomy, iPTH, Ca x P product were measured, and on two occasions at 6 weeks' intervals, anticardiolipin antibodies titer was determined, followed by a clinical monitoring of lesions of the left lower leg skin.

Results. Before parathyroidectomy, iPTH level and Ca x P product were increased, as well as IgG anticardiolipin antibody titer measured on two occasions 6 weeks apart. The histopathological analysis of the skin tissue sample of the amputated right lower leg showed mural calcification of artery walls and thrombotic occlusions of small arteries, arterioles, and dermal capillaries, in addition to epidermolysis. A week after parathyroidectomy, iPTH level and Ca x P product were within normal range. Two measurements 6 weeks apart revealed no anticardiolipin antibodies. Eight weeks after parathyroidectomy, spontaneous healing of necrotic skin lesions of the left lower leg was observed.

Conclusion. Regression of anticardiolipin antibodies, normalization of Ca x P product, and healing of the skin lesions after parathyroidectomy all pointed to the elevated PTH level as a crucial factor in the pathogenesis of CUA.

Key words: antibodies, anticardiolipin; arterioles; hyperparathyroidism, secondary; kidney failure, chronic; necrosis; parathyroidectomy; dialysis; skin

Calcific-uremic arteriolopathy is a rare syndrome that occurs in patients with end-stage renal disease (1). Most such patients have secondary hyperparathyroidism and present with a high calcium x phosphorus product. Deposition of calcium crystals in soft tissues occurs mostly in patients with a long-term hyperphosphatemia, ie, when calcium x phosphorus product is above 6 (2,3). Skin lesions are one of the first signs of the disease and may be manifested as livedo reticularis, livedo racemosa, livedoid vasculitis, or ischemic ulcerations (4). The pathogenesis of the skin lesions is still unknown. Calcific-uremic arteriolopathy is characterized by coagulation disorder and mural calcifications in small arteries and arterioles of the skin, which consequently leads to vascular thrombosis (1). Since the disease ends in skin necrosis due to calcifications of arterioles and small arteries of the skin and subcutaneous tissue, most patients have poor prognosis and many develop a fatal outcome due to uncontrollable sepsis (5). Antiphospholipid syndrome is referred to as a causative factor in the development of the livedo-type skin lesions (6).

The aim of the present case report was to show the possible role of anticardiolipin antibodies in the development of skin lesions within the complex pathogenesis in a dialyzed patient with calcific-uremic arteriolopathy.

Case report

A 68-year-old female patient has been on dialysis for 6 years due to polycystic kidney disease diagnosed 18 years ago. She had elevated levels of serum intact parathyroid hormone (iPTH) 857.7 ng/L; normal range 10-55 ng/L) and high calcium x phosphorus product (6.19; 6.41 mmol/L x 2.57 mmol/L). The patient developed bluish violet semicircular skin lesions and severe pain...
in both legs (Fig. 1A). At the same time, she complained of claudication in the right leg. Artery pulsation could not be palpated distally to the superficial thigh arteries. Necrotic ulcers of the affected regions gradually enlarged and eventually reached the size of a palm, with development of pain and exudation. Clinical picture and laboratory values suggested the diagnosis of calcific-uremic arteriolopathy. Standard X-ray of both affected regions revealed extensive calcifications of the cutaneous vascular system, including large, medium, and small blood vessels. The soft tissues beneath necrotic lesions of the skin were mostly involved. Duplex Doppler ultrasound showed marked mural calcification and obliteration of the arteries of the lower leg and bilateral lack of blood circulation distally to the common artery of the region. Titer of IgG anticardiolipin antibodies was measured twice by enzyme-linked immunosorbent assay (ELISA) and both measurements, performed 6 weeks apart, revealed elevated titers (25 and 27 GPL-U/mL, normal value <12 GPL-U/mL) (1 GPL unit = binding activity of 1 μg/mL affinity-purified IgG anticardiolipin antibodies). Increased fibrinogen levels (6 g/L; normal value 1.8-3.5 g/L) were also observed. Other coagulation parameters, including antithrombin III and protein C and S levels, were all within the normal range. Lupus anticoagulant detected by activated partial thromboplastin time (aPTT) were negative. Platelet counts were normal. Electrophoresis and immunoelectrophoresis of the serum protein were also normal. There was no oxalemia. Antinuclear and anti-DNA antibodies were not found. Alkaline serum phosphatase level was above the normal range (184 U/L; reference range 64-153 U/L). Markers of hepatitis B and C and antibodies to human immunodeficiency virus (HIV) type 1 and type 2 were negative by enzyme immuno-assay. The patient was treated with a low-molecular-weight heparin (nadroparine calcium, 0.6 mL, subcutaneously), analgesics, and antibiotics locally for necrotic skin lesions. The duration of hemodialysis was extended to 5 h, with a reduced calcium concentration in the dialyze (1.5 mmol/L). The general state of the patient worsened, necrosis of the right lower leg gradually advanced, and marked signs of severe ischemia of the right lower leg appeared. Two months after the first skin lesions appeared, the patient had to undergo below-knee amputation of the right leg. Histopathologic examination of a skin specimen taken from the edge of gangrenous lesion of the amputated leg revealed suppurative necrotic foci, with calcification of arterioles of the subcutaneous tissue. One of the specimens showed a thrombus of the artery with marked obliteration of the artery lumen, which was also narrowed by a series of plaques (Fig. 2).

One month after the amputation, the patient underwent total parathyroidectomy. Postoperatively, a significant decrease in iPTH levels (10 ng/L) was observed, and normalization of calcium×phosphorus product was obtained. Just a week after surgery, the calcium×phosphorus product was as low as 2.72 (2.29 mmol/L×1.18 mmol/L).

Histopathology of all four extirpated parathyroid glands showed nodular hyperplasia; and adenoma was found in two of them. The pain in the right lower leg disappeared two weeks after parathyroidectomy, and spontaneous healing of necrotic skin lesions started. Eight weeks after parathyroidectomy the skin necrosis was completely replaced by scar formation (Fig. 1B). For this reason, low-molecular-weight heparin administration was terminated. Two months after

Figure 1 A. Dialyzed patient with calcific-uremic arteriolopathy before parathyroidectomy. Livedo-type skin lesions on both lower limbs. B. Left lower limb skin lesion in the same patient 8 weeks after parathyroidectomy.

Figure 2. The artery of the amputated leg with intraluminal thrombus and extensive calcification within the arterial walls, with cracking artifacts (x10).
surgery, no anticardiolipin antibodies were found on two measurements performed 6 weeks apart.

Discussion

Livedo reticularis is the most common initial skin manifestation of calcific-uremic arteriolopathy. It may advance progressively and end up in necrotic gangrene, just as was the case with our patient. In case of secondary bacterial infection, gangrene that can develop may be a life-threatening condition. In addition to calcific-uremic arteriolopathy, wound healing in a patient with end-stage renal disease may be compromised by anemia, hypoalbuminemia, interstitial edema with the response to inflammatory reaction or hypervolemia (7), repeated local trauma (8), immunosuppressive therapy (9), and intravascular thrombosis (10). None of these factors was observed in our patient, except for circulation disorder of the lower leg vessels, confirmed first by duplex Doppler ultrasound and then by histopathologic examination of the blood vessels of the amputated extremity. Histopathology of the skin lesions showed mural calcifications of arterioles and small arteries, as well as occlusions of the arterioles and dermal capillaries, including thrombi and ischemic epidermolysis. Thrombosis of small blood vessels associated with calcific-uremic arteriolopathy points to the possible hypercoagulability. The exact pathogenesis of the skin lesions occurring in the patients with end-stage renal disease and calcific-uremic arteriolopathy still remains unclear. Calcium is supposed to have a direct cytotoxic effect on endothelial cells of the blood vessels, consequently inducing damage to the vessels and increase in selectin and adhesin expression on the surface of endothelial cell membrane, which leads to thrombocyte aggregation on damaged endothelial sites and microthrombus formation (5,11). Microthrombus formation is closely related to conditions associated with blood hypercoagulability, such as lack of C and S proteins, hyperfibrinogenemia, or the presence of lupus anticoagulant or anticardiolipin antibodies (12). Livedo reticularis is a type of cutaneous lesion that may also follow conditions other than calcific-uremic arteriolopathy, e.g., vasculitis of varying etiology, disseminated intravascular coagulation, cholesterol embolization of small blood vessels, cryoglobulinemia, lymphoproliferative diseases, hyperoxalemia (13), HIV infection (14), coumarin-based anticoagulant therapy (15), lack of C and/or S proteins (16,17), and antiphospholipid syndrome. Despite the presence of calcific-uremic arteriolopathy, it is necessary to exclude any of the factors with detailed diagnosis of livedo reticularis. The increase in fibrinogen level found in the patient was most likely associated with local inflammatory process in the lower leg regions.

Negative lupus anticoagulant and anticardiolipin antibodies excluded the correlation between the skin lesions and presence of antiphospholipid syndrome.

The antiphospholipid syndrome is a multisystem disorder of hypercoagulation. Anticardiolipin antibodies and lupus anticoagulant may directly cause thrombosis. Phospholipid specificity of the antibodies assumes a central role in their pathogenetic actions, which include endothelial cell damage, interference with production and release of prostacyclin by endothelial cells, activation of platelets, interference with the protein C and S pathways, and interference with antithrombin III activity (18). β2-glycoprotein that appears on the membrane surface of the damaged endothelial cells enhances binding of anticardiolipin antibodies to phospholipids and may be responsible for the development of the syndrome (18). The antiphospholipid syndrome has been classified into primary or secondary syndromes, and may occur along with some other disease. Skin manifestations commonly appear as the first sign of the disease, and are usually associated with recurrent thrombotic events (arterial and/or venous), repeated fetal loss, or thrombocytopenia.

Up to 2% of healthy persons have detectable lupus anticoagulant or anticardiolipin antibodies, and in 0.2% of the population the titer is high (19). The elements that should be present to make the diagnosis of antiphospholipid syndrome include recurrent thrombotic events, repeated fetal loss, thrombocytopenia, and constantly elevated titer IgG anticardiolipin antibodies or lupus anticoagulant. Also, at least one clinical and one serologic feature should be present, with serologic feature positive on more than one occasion and measured at least 6-8 weeks apart. Other features suggestive of the syndrome include transient high titer IgG anticardiolipin antibodies, sustained or high titer IgM anticardiolipin antibodies, or low titer of either IgG or IgM isotope. Primary antiphospholipid syndrome is more common than the secondary syndrome. Secondary antiphospholipid syndrome is associated with a large spectrum of diseases including systemic lupus erythematosus, other autoimmune diseases, malignancy, particularly lymphoproliferative disorders, infections (e.g., syphilis, HIV, hepatitis C, borreliosis) and drug ingestion (e.g., chlorpromazine, procarbazine, and interferon). End-stage renal disease treated with hemodialysis is referred to as one of the causative factors of secondary antiphospholipid syndrome (6). Other possible causes of the disease were excluded in our patient by proper diagnosis. An elevated IgG anticardiolipin antibodies titer was found on two occasions, in measurements performed 6 weeks apart.

We found reports on spontaneous healing of gangrene skin lesions following parathyroidectomy (5,7). Parathyroidectomy in our patient was followed by a decrease in iPTH concentration, normal calcium and phosphate values, and normalization of calcium x phosphorus product. Two months after the surgery, spontaneous healing of necrotic skin lesions of the left lower leg was also observed. No anticardiolipin antibodies were found on that occasion. The same results were obtained 6 weeks later. Two repeatedly negative anticardiolipin antibodies reports excluded persistent presence of anticardiolipin antibodies in our patient.

In conclusion, calcific-uremic arteriolopathy rarely occurs in patients on hemodialysis who have developed either secondary and/or tertiary hyperparathyroidism with a high calcium x phosphorus prod-
Skin lesions in the context of calcific-uremic arteriolopathy may heal spontaneously and may be completely cured with total parathyroidectomy, if timely performed, and with a low-molecular-weight heparin therapy. The appearance of anticardiolipin antibodies is also possible in patients with calcific-uremic arteriolopathy as epiphenomenon, which largely contributes to the occurrence of dermal lesions. Regression of anticardiolipin antibodies, favorable clinical course of the disease, and normalization of calcium x phosphorus product were observed after parathyroidectomy. In our patient, the elevated iPTH concentration was but one of several causative factors, which had an impact on skin necrosis. Parathyroidectomy and subsequent decrease of elevated iPTH concentration was sufficient to stop the pathologic process, indicating the importance of iPTH for the complexity of pathogenetic chain of the disease.

References

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