Russian Journal of Clinical Dermatology and Venereology =
Klinicheskaya dermatologiya i venerologiya 2018, vol. 17, no 6, pp. 33-37
https://doi.org/10.17116/klinderma20181706133

Calciphylaxis: a case of idiopathic disease of the penis with favorable outcome

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ABSTRACT
Calciphylaxis is a rare syndrome characterized by deposition of calcium salts in soft tissues and blood vessels with subsequent ischemia, necrosis of the skin and underlying areas. Here we provide a literature review on the history, etiology, pathogenesis, clinical presentation, diagnosis, risk factors, course, treatment, and prognosis of the disease under study. The main clinical manifestations of isolated calciphylaxis of the penis include formation of painful violet and bluish-red nodules and/or nodes characterized by round or irregular shape and localized mainly on the balanus. Later on, development of necrosis and ulcers of irregular shape is observed in these areas, which are then replaced by rough scars. The diagnosis can be established based on clinical presentation, medical history, and high levels of calcium and phosphorus in the blood serum. Calciphylaxis is extremely rare in patients with normal calcium level. The diagnosis is verified using pathological examination, which shows deposition of calcium salts in the skin and soft tissues. Here we report our own clinical observation of penile idiopathic calciphylaxis in a patient with normal blood levels of calcium and phosphorus.

Keywords: *calciphylaxis, clinic, pathomorphology, differential diagnosis, treatment.*

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TO CITE THIS ARTICLE:
Sedova TG, Elkin VD, Mitryukovsky LS, Myasnikova MB. Calciphylaxis: a case of idiopathic disease of the penis with favorable outcome. *Russian Journal of Clinical Dermatology and Venereology=Klinicheskaya dermatologiya i venerologiya*. 2018;17(6):33-37. (In Russ.).
https://doi.org/10.17116/klinderma20181706133

Calciphylaxis (CP, also known as calcific uremic arteriopathy) is a rare syndrome that is characterized by extensive or local calcium deposits in peripheral arteries and soft tissues, which causes vascular stenosis and obstruction, ischemia, and necrosis of the skin and underlying tissues. The disease mainly affects distal parts of the extremities, buttocks, thighs, and trunk. Other localizations of CP are extremely rare [1–4]. An unfavorable prognosis and high mortality are characteristic of patients with involvement of proximal blood vessels in the pathological process [5].

The disease was first mentioned in the middle 19th century when R. Virchow first noted a potential relationship between chronic kidney disease and soft tissue calcification. According to H. Selye, these skin lesions are associated with acquired hypersensitivity to calcification [3]. Later, the term "calciphylaxis" was coined, which has been used until the beginning of the 21st century. There is a pathogenic relationship between the disease and chronic renal failure; the prevalence of CP in the setting of chronic renal failure varies from 3 to 83% [1, 6, 7]. In this regard, some researchers believe that the term "calciphylaxis" has lost its significance and should be replaced with the term "calcific uremic arteriopathy" [1]. However, the established disease name continues to prevail in the literature.

CP clinically presents with ischemic foci in the form of dark red/purple patches of various size and extension in the distal lower extremities (usually on the posterior and lateral surfaces of the legs), thighs, buttocks, genitals, abdomen, and, less often, other areas [4, 5]. In the affected areas, there is painful induration of soft tissues, sometimes combined with blisters, later followed by the development of necrosis, rejection of necrotic tissues, and formation of irregularly-shaped ulcers [1, 2, 4, 6].

In addition to chronic kidney disease (especially in patients with end-stage renal disease who are under long-term hemodialysis), the risk factors for CP include diabetes mellitus, pathological obesity, hypoparathyroidism, hyperparathyroidism, and some other factors, such as the use of corticosteroids, heparin calcium salt, vitamin D preparations, iron-dextran complex, etc. [7–13].

The prognosis for CP is unfavorable in many cases due to the development of phlegmon and sepsis. A number of publications have reported that biopsy aggravates the prognosis [1, 12].

Often, penile lesions are combined with CP of various localizations, and there are very few reports of the isolated form (only 40 cases), which sometimes results in self-amputation of the organ and/or a fatal outcome [1, 8].

CP usually affects the glans penis and less often the penile shaft. Clinical manifestations are represented by

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nodules merging into single plaques; isolated rounded, oval, or polycyclic nodes of 0.5 to 2–3 cm in diameter. Larger lesions are extremely rare. The color of the affected skin over lesions varies from small areas of livedo reticularis to purple, purple-red, and bluish-red patches [1, 2, 4, 5, 7]. Over time, the affected areas are indurated and necrotized, and refractory ulcers and fistulas with fibrinopurulent discharge are formed [10–14]. The necrotic areas may be further infected, which may lead to sepsis and/or death [1, 15–17]. In rare cases, an isolated penile lesion simulates the clinical signs of invasive squamous cell carcinoma [18]. In favorable situations, the process ends with the formation of gross cicatricial changes [1].

The diagnosis can be made based on the clinical presentation, medical history, and high levels of calcium (more than 2.6 mmol/L) and phosphorus (more than 1.5 mmol/L) in the blood serum. According to various sources, the normal calcium level should be 1.5–2-fold higher than that of phosphorus. In CP, the level of calcium increases 70-fold or more compared to that of phosphorus. In rare cases, CP of the skin and soft tissue may occur at normal values of blood calcium [1]. Additional diagnostic techniques are X-ray, dopplerometry, and magnetic resonance angiography. The diagnosis is verified by pathomorphological examination that reveals intimal hyperplasia and calcification of the subcutaneous arteries, skin, and soft tissues as well as ischemic necrosis [1, 6, 13, 15]. However, it should be borne in mind that biopsy poses a high risk of exacerbation and further progression of CP [1].

Treatment of penile lesions remains controversial. A mandatory requirement is elimination of risk factors [16, 17]. The management of patients includes conservative treatment with local wound care and debridement of focal infection foci. Surgical treatment is used very rarely: it involves partial or complete penectomy. This option can be used for patients with severe infection, extensive gangrene, and severe pain unalleviated by opiates and analgesics [1, 18–23]. The efficacy of partial and total parathyroidectomy is also disputed in the literature. Improvement of the condition and prognosis is achieved through preferred use of conservative treatments for secondary hyperparathyroidism [13, 14]. In addition to the standard conservative and surgical treatments, patients undergo systemic antibiotic therapy, intravenous infusion of sodium thiosulfate, application of bisphosphonates, and hyperbaric oxygenation [1, 9, 22].

Therefore, it may be stated that CP with an isolated penile lesion is a rare condition that requires identification and elimination of potential risk factors.

As an illustration, we present a clinical case of penile CP.

A male patient V., born in 1985, was referred from the Regional Oncologic Dispensary to the Polyclinic of the Regional Dermatovenerologic Dispensary with suspected syphilis. According to the medical history, an eruption (ulcer) on the penis developed a few months ago. The patient experienced moderate pain. After consulting to a dermatovenereologist at the place of residence, the patient was referred to the Perm Regional Oncologic Dispensary with a presumptive diagnosis of squamous cell carcinoma of the penis, where he was treated for 10 days.

According to the medical records from Oncologic Dispensary, no significant visceral pathology was found during general and physical examination of the patient. The epidemiological, allergic, and hereditary history was unremarkable. There were no adverse professional factors.

Local status: there was a limited, asymmetrical, and sub-acute inflammatory pathological skin process localized predominantly on the skin of the glans penis and preputium. The affected area was represented by an indurated edematous erythematous plaque of a livid tint and isolated, up to 0.8 cm in diameter, nodules localized in soft tissues of the preputium. On palpation, the nodules were moderately tender and dislocated with respect to the surrounding tissues. In the center of the plaque, there was a bright pink ulcer with irregular undermined edges. The bottom of the ulcer was indurated and tuberous, with scanty serous discharge. The preputium was swollen, pink-purple, and elastically indurated. There were multiple telangiectasias on the inner leaf of the preputium. Fibrin deposits were present in the coronal sulcus area **(Fig. 1)**. The inguinal lymph nodes were enlarged to 1 cm. The lymph nodes were elastically indurated, tender on palpation, and not matted to each other; the skin over the nodes was unchanged.

According to the clinical and laboratory examination of the patient, the common clinical indicators were within the age norm. Blood chemistry panel: glucose — 4.38 mmol/L; creatinine — 101 mmol/L; total protein — 68 g/L; albumin — 43.7 g/L; aspartate aminotransferase — 26 U/L; alanine aminotransferase — 44 U/L; total bilirubin — 11.39 μmol/L; potassium — 4.01 mmol/L; calcium — 1.17 mmol/L; phosphorus — 1.2 mmol/L; sodium — 137.2 mmol/L.

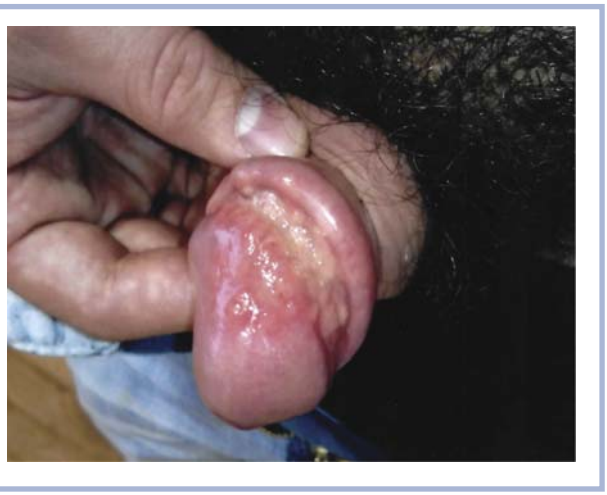

Fig. 1. **Ulcerative defect on the balanus, isolated nodules at the foreskin, multiple telangiectasias, fibrin.**

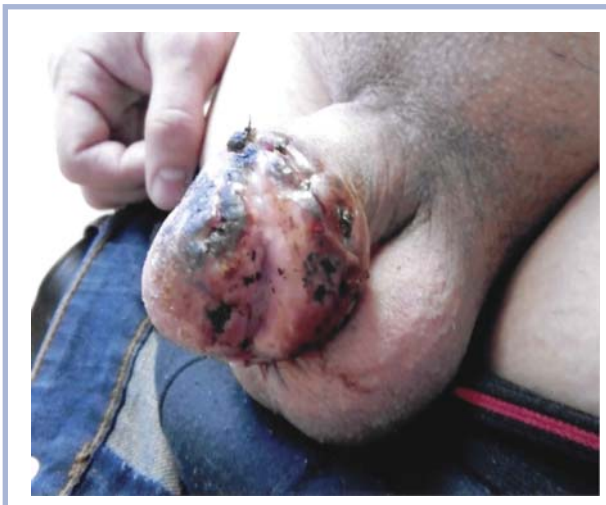

Fig. 2. **Condition after circumcision and biopsy of the balanus.**

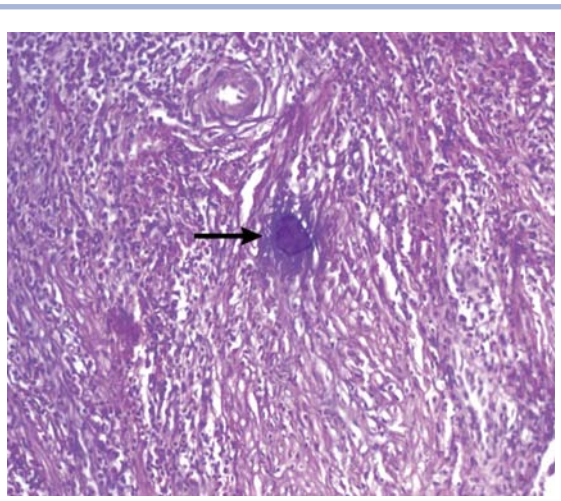

Fig. 3. **Histological picture: massive polymorphic cell infiltrate with admixture of lymphocytes and leukocytes in the dermis, calcium deposition (arrow).**
Hematoxylin and eosin stain (magnification 200).

Electrocardiogram: sinus rhythm; left bundle branch block.

There were no antibodies to intestinal worm and protozoa eggs. Serological markers of hepatitis, HIV, and syphilis were negative. Radiography and ultrasound of the abdominal organs and kidneys revealed no pathology. Consultation with related specialists (therapist, ophthalmologist, neurologist, cardiologist, surgeon, endocrinologist) revealed no associated somatic diseases.

To verify the diagnosis, the patient underwent circumcision and a skin biopsy of the penis glans (**Fig. 2)** at the Perm Regional Oncologic Dispensary. There were no histological signs of a malignant process in the biopsy; the patient was discharged from the Dispensary and referred to the Regional Dermatovenerologic Dispensary with suspected syphilis.

Upon consultation at the Regional Dermatovenerologic Dispensary, we identified a clinical picture that corresponded to the medical records from Oncologic Dispensary, but had obvious signs of epithelialization and initial cicatricial changes in the ulcer area on the penis glans. Suspected CP was confirmed by a pathologist upon re-examination of the specimens. The pathomorphological picture of pathological areas was characterized by thickening of the epidermis with pronounced acanthosis and without atypia. There was extensive ulceration in the center of the epidermal layer. In the dermis, there were single dark purple calcium deposits of irregular shape and different size. A massive (predominantly eosinophilic) polymorphic cell infiltrate containing lymphocytes and leukocytes was observed subepidermally. Vasculitis was present **(Fig. 3)**.

Conclusion

The presented clinical case is a rare idiopathic form of penile CP. The diagnosis is confirmed by a typical clinical picture and laboratory, pathomorphological, and common clinical findings. A distinctive feature of idiopathic CP is an isolated lesion of the genital organs in young healthy males with normal levels of calcium and phosphorus in the blood serum. However, a high risk of recurrence and involvement of internal organs in the pathological process requires careful follow-up of these patients by doctors of related specialties.

Authors' contributions:

Data collection — M.B. Myasnikova, L.S. Mitryukovsky

Data interpretation — T.G. Sedova

Drafting the manuscript — T.G. Sedova

Revising the manuscript — V.D. Elkin, L.S. Mitryukovsky

The authors declare no conflict of interest.

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Received 17.11.2017
Accepted 11.10.2018