Case report

Tumoral calcinosis: Diffuse multifocal form in hemodialysis patients. Two case reports

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A R T I C L E   I N F O

Article history:
Received 4 April 2015
Accepted 17 January 2017

Keywords:
Tumoral calcinosis
Extra-articular calcification
Severe hyperparathyroidism

A B S T R A C T

Orthopedic surgeons are often consulted for diagnosis of MASS syndrome, imaging showing periarticular calcification, or joint stiffness. Such presentations in a dialyzed patient should suggest tumoral calcinosis, which is a rare complication of dialysis, often diagnosed wrongly or late. It is often associated with calcium phosphate balance disorder, in which treatment is difficult and must take account of known contributing factors: severe hyperparathyroidism, increased phosphocalcic product, therapeutic calcium and vitamin D overload, and bone turnover slowed for varying reasons. We report a clinical, radiological and therapeutic description of two cases of tumoral calcinosis, which consists in deposits of hydroxyapatite, the crystalline form of calcium phosphate, in diffuse multifocal periarticular locations, inducing both aesthetic and functional damage.

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1. Introduction

Orthopedic surgeons are frequently consulted for mass syndromes or periarticular calcifications causing esthetic blemish, joint stiffness or even functional impotence. In dialysis patients, these calcifications correspond to cutaneous calcinosis: soft-tissue calcification by deposition of hydroxyapatite, the crystalline form of calcium phosphate in the skin. Crystallization progressively induces relatively complex structures, constituting ossification [1]. Calcinosis may be isolated (localized) or multiple (diffuse multifocal), and small or so extensive as to represent a tumoral mass known as tumoral calcinosis, of idiopathic or secondary etiology. Pathologic examination differentiates between calcinosis and ossification and can identify the calcic nature of the crystals by two particular stains: von Kossa and alizarin crimson. Extracutaneous calcification is increasingly found in dialysis patients, in whom life expectancy has increased thanks to renal replacement therapy, but the pathogenesis of diffuse multifocal tumoral calcinosis is not well understood and management is poorly codified. We report two cases of tumoral calcinosis with multiple extra-articular and articular involvements, to shed light on diagnosis and discuss the particular case of patients under dialysis.

2. Case reports

2.1. Case 1

A 26-year-old man, under chronic hemodialysis for 2 years for IgA nephropathy with right radial fistula and no particular medical history, had been experiencing inflammatory joint pain in small and large joints, progressing toward hot painful periarticular masses, soft in some places and tending toward abscess and fistula without other non-renal signs (Fig. 1).

Clinical examination and morphologic assessment, including plain X-ray, CT of the affected joints, bone scintigraphy and Tc-99m MIBI scintigraphy found largely calcified multilobular periarticular masses with massive infiltration of the hypodermis and shoulder, elbow, knee, metacarpal and metatarsals muscles and hip and inter-phalangeal joints (Figs. 1a, c, 2, 3).

He showed tertiary hyperparathyroidism at 898 pg/mL, hypercalcemia at 109 mg/L (85–101 mg/L), hyperphosphatemia at 82 mg/L (25–49 mg/L), phosphocalcic product at 8938 mg²/L², 25-hydroxy vitamin D at 241U/mL and normal total alkaline phosphatase (Table 1).

In view of the inflammatory and multiple nature of the periarticular masses, etiologic assessment was conducted. Serum protein electrophoresis, infection work-up (peripheral hemoculture, HIV, syphilis and hepatitis B and C serology, phthisiologic work-up and tuberculin skin-test for tuberculosis infection) and immunology (screening for ankylosing spondylitis, antineutrophil cytoplasmic,
anti-DNA, anti-nuclear and anti-Scl 70 antibodies) were negative; skin biopsy found cutaneous and muscular calcium deposits (Table 2).

The patient underwent daily dialysis (6 × 4 hours) by calcium-depleted electrolytic bath (1.37 mmol/L) followed by 7/8th parathyroidectomy. Pathology showed ablation of 3 hyperplastic parathyroid glands; complementary 99m Tc-MIBI scintigraphy found no cerebral, thoracic or abdominal ectopic fixation related to ectopic parathyroid glands.

Progression showed correction of phosphocalcic parameters, with normalized calcemia and phosphatemia, postoperative parathyroid hormone assay at 31 pg/mL and, above all, spectacular regression of calcinosis size as of day 15, with the elbow calcinosis shrinking from 8 cm to 9 mm and complete resolution of the 10-cm shoulder calcinosis. Function was restored in both joints. At 26 months’ follow-up, there was no recurrence (Fig. 1b and d).

2.2. Case 2

A 56-year-old man, under dialysis for 8 years for vascular nephropathy, was referred for disabling inflammatory periarticular masses of more than 2 years’ progression, deforming the shoulder and knee, which had been treated as infected necrotizing synovitis, without clinical improvement (Fig. 4).

Clinical examination and morphologic assessment on plain X-ray and 99m Tc-MIBI scintigraphy found poorly delineated...
multilobular calcic formations invading the shoulder and knee joints (Fig. 5a and b).

Biological examination found tertiary hyperparathyroidism at 1489 pg/mL, hypercalcemia at 111 mg/L, hyperphosphatemia at 86 mg/L, phosphocalcic product at 9546 mg²/L², 25-hydroxy vitamin D at 21 IU/mL and normal total alkaline phosphatase (Table 1). Infection work-up and immunologic screenings for underlying pathology were non-contributive.

Treatment comprised 7/8th parathyroidectomy, pathologic examination finding ablation of 3 hyperplastic parathyroid glands and of half of the left inferior gland. Dialysis was performed by calcium-depleted electrolytic bath (1.37 mmol/L) at 16 hours per week.

Progression showed hypocalcemia at 69 mg/L postoperatively, normal phosphatemia, and parathyroid hormone at 25 ng/mL. There was 80% regression of the periartricular masses at 3 weeks, with elbow and knee calcinosis decreasing from 15 and 11 cm to 3 and 2 cm, respectively, and complete functional recovery (Fig. 5c). At 2 months, the patient developed secondary hyperparathyroidism, with parathyroid hormone level rising to 687 ng/mL, calcemia at 89 mg/L and phosphatemia at 57 mg/L. 99mTc-MIBI scintigraphy found no ectopic parathyroid parenchyma. Phosphorus chelator supplementation and 60 mg/day cinacalcet calciimimetic maintained parathyroid hormone levels between 200 and 400 pg/mL. At 12 months’ follow-up, there were no signs of mass aggravation or new lesions.

3. Discussion


Revelation is often based on a periarticular tumoral mass involving small and large joints, of variable size, sometimes inducing severe deformity and esthetic blemish, causing joint stiffness or functional impotence.

Tumoral calcinosis may be asymptomatic or induce painful inflammatory episodes and lesions liable to ulcerate, allowing transepidermal elimination of the calcic material, as in our first case. It may also lead to functional impairment and compression-related complications and superinfection, sometimes with general signs, as in our second case [5,6]. Neurovascular compression has been reported [4,7].

Clinically, tumoral calcinosis presents as single or multiple superficial or deep hard caseous nodules with whitish or yellowish content, often larger than 3 cm [7], mainly located periarticularly, especially around the shoulder, hip, elbow, wrist, hand, foot or sternoclavicular joints [4,7]. In the present two cases, size exceeded 10 cm, and locations were multiple.

Radiology finds radio-opaque images [1] suggestive of calcium, and an irregularly delineated multilobular aspect. Plain X-ray is often sufficient, but complementary CT or MRI imaging of the joint may be necessary to assess mass extension with respect to neighboring neurovascular structures in case of compressive syndrome.

Biological work-up comprising calcemia, phosphatemia, intact parathyroid hormone and 25-hydroxy vitamin D2-D3 assay assesses phosphocalcic status in dialysis patients, completed by other examinations to assess the secondary causes, detailed below, according to interview and clinical context.

Tumoral calcinosis is an unusual lesion, which may be primary (hereditary) or secondary.

The primary form implicates recessive autosomal mutations of 3 genes involved in phosphate metabolism: FGF23, GALNT3 and KL [3].

Secondary forms are due either phosphocalcic metabolism abnormality or to other abnormalities [8]:

- exogenous medical or iatrogenic calcinosis secondary to perfusion, notably in neonates, calcium alginate dressings in graft patients, or multiple subcutaneous and intramuscular injection;
- exogenous occupational calcinosis, secondary to traumatic penetration by calcium salts, which may be accidental or occupational: calcium chloride, used for road de-icing and found in mine water and in the petroleum industry;
- traumatic calcinosis, secondary to skin abrasion or physical trauma (by needle, catheter, cannula, etc.), sometimes occurring decades after radiation therapy, electrification, exposure to cold or burns, or following multiple surgeries;
- calcinosis secondary to inflammatory lesions, venous insufficiency, phlebothis, vascular deformity or hematoma;
- calcinosis secondary to infectious lesions: bacterial (leprosy), parasitic (cyticercosis, filariasis – dracunculiasis, onchocerciasis or “river blindness”, loiasis or Bancroft filariasis – hydatidosis, trichinosis), viral (herpes simplex, herpes zoster), or mycotic;

Table 1

<table>
<thead>
<tr>
<th>Biological parameters at start of treatment</th>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td>PTHI pg/mL</td>
<td>898</td>
<td>1489</td>
</tr>
<tr>
<td>Calcemia mg/L</td>
<td>109</td>
<td>111</td>
</tr>
<tr>
<td>Phosphatemia mg/L</td>
<td>82</td>
<td>86</td>
</tr>
<tr>
<td>Phosphocalcic product mg²/L²</td>
<td>8938</td>
<td>9546</td>
</tr>
<tr>
<td>25-hydroxy vitamin D2-D3</td>
<td>24</td>
<td>21</td>
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<tr>
<td>Alkaline phosphatase IU/L</td>
<td>65</td>
<td>56</td>
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Table 2

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<thead>
<tr>
<th>Etiologic assessment</th>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td>Hemoculture</td>
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<tr>
<td>Serology</td>
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<td>HIV</td>
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<td>Hepatitis B</td>
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<td>Syphilis</td>
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<td>Phthisiologic assessment</td>
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<td>Intradermoreaction</td>
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<tr>
<td>Immunologic assessment</td>
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<tr>
<td>Anti-CCP</td>
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<td>–</td>
</tr>
<tr>
<td>Anti-DNA antibodies</td>
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<td>–</td>
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<tr>
<td>Anti-nuclear antibodies</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anti-scleroderma antibodies</td>
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<td>–</td>
</tr>
</tbody>
</table>

–: normal.
tumor or cyst calcification;
• connective tissue calcinosis: notably CREST syndrome (calcinosis cutis, Raynaud’s phenomenon, esophageal dysfunctions, sclerodactyly and telangiectasia), polymyositis, dermatomyositis, or systemic erythematous lupus.

Tumoral calcinosis is a rare complication of terminal chronic kidney failure under dialysis, with prevalence between 0.5% and 3% [9,10]. The affected arterial and periarterial sites are constituted of hydroxyapatite [11]. Treatment is difficult, and has to take account of the main known risk factors:

• hyperphosphatemia, which is difficult to control due to poor compliance with diet and with regular chelator medication;
• insufficient dialysis.

Hyperphosphatemia further induces phosphocalcic product elevation and severe hyperparathyroidism.
Deposition of hydroxyapatite, the crystalline form of the phosphocalcic complex in soft tissue, is no longer seen as a purely passive phenomenon related to elevated calcemia and/or phosphatemia [6,12]. Involvement of an active local process requiring specific cells and proteins has been experimentally proved in transgenic mice as far as vascular calcification is concerned, and is conceivable for periarticular calcification as well [9]. Extraosseous mineralization is involved as follows: various stimuli induce differentiation of certain vascular wall or soft-tissue cells into osteoblasts; protein accumulation or depletion respectively enhances or inhibits the calcification process; and a matrix is formed, undergoing mineralization causing soft-tissue calcification and thus tumoral calcification.

Several risk factors have been identified, and notably hyperparathyroidism, which mobilizes bone calcium, inducing osteopenia. Persistent vitamin D deficit induces bone resistance to parathyroid hormone, so that hypocalcemia cannot be corrected, thus aggravating the hyperparathyroidism. In kidney failure, phosphocalcic product exceeding 5.8 mmol/L² accounts for the tendency for soft-tissue calcification to form.

Adynamic osteopathy, secondary either to subtotal parathyroidectomy or to excessive treatment by vitamin D derivatives, calcium carbonate and/or aluminum, induces low bone remodeling and is a frequent cause of calcification [5,11].

Taken together, these factors disturb phosphocalcic levels, inducing anaric soft-tissue and intravascular calcium phosphate complex deposition, probably aggravated iatrogenically by excessive attempts to correct hypocalcemia by calcium or vitamin D supplementation or by non-respect of low-phosphorus diet.

It is important to distinguish calcification from calciphylaxis (also known as calcific uremic arteriolopathy), which is a rare disease with particularly severe progression, mainly affecting patients under dialysis (hemodialysis or peritoneal dialysis) for kidney failure, with onset at a mean 30 months after initiation of dialysis or sometimes after kidney transplantation. It involves small to medium sized calcifications in the vascular media, deep dermis or hypodermis, unlike calcification, which affects soft tissues. It causes ulcer-crotic, purpuric, livedoid and hyperaletic lesions with impaired bone and mineral metabolism, notably hyperparathyroidism. Mortality is high: 60–80% in proximal and 20–30% in distal locations. The pathophysiology is not fully understood: chronic kidney failure seems not to be the only factor, as calciphylaxis is increasingly reported in other cases, such as neoplasia (breast cancer, cholangiocarcinoma and melanoma), primary hyperparathyroidism, antivitamin K treatment, vitamin D overdose, cirrhosis without kidney failure, and obesity [13].

There are numerous treatments for uremic tumoral calcification, but results are not always adequate.

Regression of calcification can be achieved within a few months by treatment targeting a known risk factor: low-phosphorus diet or phosphorus chelators and cessation of calcium and vitamin D intake have shown a certain efficacy, and can serve as adjuvant therapy [7,9,12]; efficacy, however, is variable, testifying to the complexity of the pathophysiology. Treatment by 1.37 mmol/L calcium-depleted bath has therefore been suggested, and above all increasing weekly dialysis time to more than 2 hours [7].

Subtotal parathyroidectomy has given spectacular results in some cases, especially of severe hyperparathyroidism: Benkert et al. and also Cohen and Parikh reported complete regression and dissolution of tumoral calcification [14], as in our first case.

Other authors, however, reported incomplete regression, as in our second case; but follow-up was insufficient to indicate failure, recurrence or even aggravation [4]. Onset of secondary hyperparathyroidism in our second patient led us to complete therapy by hygiene and dietary measures and especially by the non-calcific phosphorus chelator sevelamer, and calcimetric treatment.

Kidney graft has been reported to be effective in quickly resolving tumoral calcification, without risk of relapse [4]. In patients under peritoneal dialysis, daily calcium-depleted dialysate at 2.5 mmol/L seemed effective in a series of patients, and associated hemodialysis sessions by calcium-depleted bath seemed to enhance results [15].

Other treatments have also been tried: bisphosphonates (mainly pamidronate) in terminal kidney failure patients with secondary or tertiary hyperparathyroidism, where intravenous pamidronate gave complete regression of scapular calcification in 6 months [16].

Sodium thiosulfate, an antioxidant and calcium chelator, seems promising, especially in calciphylaxis. Intravenous administration at 12.5 to 25 mg following each dialysis for 11 to 14 months gave rapid resolution of pain and functional impotence and partial or total regression of the tumoral calcification, without recurrence at 1.5 to 12 years’ follow-up. Topical application at 25% has been developed in some cases and series of dystrophic calcification, with encouraging results [17].

The efficacy of these techniques in primary prevention cannot be assessed, as the disease is not systematic in dialysis patients with abnormal phosphocalcic metabolism. We nevertheless consider it advisable whenever possible to optimize management of mineral and bone disorder in patients with chronic kidney failure under dialysis, to protect against onset of calcification.

Surgical treatment of tumoral calcification is functional in its objectives and is only palliative. It is considered when response to other treatment is insufficient [18]. It is difficult surgery, with risk of recurrence, faster progression if resection is incomplete, infection or even ulceration of the lesion [4].

4. Conclusion

Tumoral calcification is fairly rare, but incidence is increasing with increasing life expectancy in patients under dialysis and increasing rates of risk factors; 7/8th subtotal parathyroidectomy and calcium-depleted bath dialysis procure regression of the mass, but adjuvant treatment to reduce phosphatemia or resurgence of hyperparathyroidism is often necessary. Surgery is difficult, and no more than palliative. Sodium thiosulfate seemed highly promising in some small series, and further studies are awaited to assess its role in managing tumoral calcification in dialysis.

Disclosure of interest

The authors declare that they have no competing interest.

References


