



## Multiple Metastatic Calcification in a Patient with Secondary Hyperparathyroidism: Regression after Parathyroidectomy - A Case Report and Literature Review

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### Abstract

We present a case of multiple metastatic calcifications in a uremic patient on maintenance hemodialysis for 8 years. Unusually, in our patient the metastatic calcification with Metastatic Pulmonary Calcification (MCP), vascular calcification, soft tissue calcification surrounding large joint and calcific uremic arteriopathy. He underwent parathyroidectomy for secondary hyperparathyroidism. Five months after surgery a rapid regression of MCP and soft tissue calcification was observed, but calcific uremic arteriopathy keep progressive development.

### Case Presentation

A 43-year-old man with uremia due to glomerulonephritis, receiving hemodialysis since 2010, three times per week, four hours per time, was presented with ulcer of left heel for 1 month. He found a swelling over the right shoulder joint in early 2011. The swelling was mobile and soft, and grew rapidly from 2 cm to 10 cm in five months, but he had neither pain nor skin changes. There was no special treatment or regular examination of serum calcium, phosphorus and intact Parathyroid Hormone (iPTH). Over the next two years, another swelling developed over the left elbow joint similar to the ones described for the right shoulder joint. He hospitalized for lumbosacral area and bower limbs pain in July 2016. Blood tests revealed: (iPTH) 2156.5 pg/ml (<72 pg/ml). Computed Tomography (CT) scans showed bilateral, diffuse, centrilobular, ground-glass opacities areas distributed in the upper lobes (Figure 1). He was diagnosed with uremic renal osteopathy and uremic pulmonary metastatic calcification. There was no significant decrease in iPTH level after treatment with calcimimetics for 2 months. The lumbosacral area and bower limbs pain still progresses. He was difficulty in walking by the end of 2017. One year later, the patient returned to our hospital with the complaint of severe pain in left heel. In the past eight years, his height has been shortened by 6 cm and his weight has dropped by 20 kg.

Physical examination on admission showed: Emaciated form, a blood pressure of BP 144/96 mmHg, a pulse rate of 90/min, a body temperature of 36.5°C and a respiratory rate of 28/min. Two irregular, hard masses were found around right shoulder joint and left elbow joint. Joint range of

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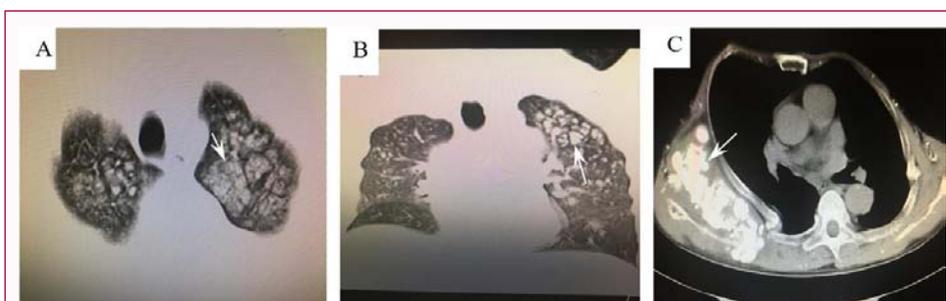
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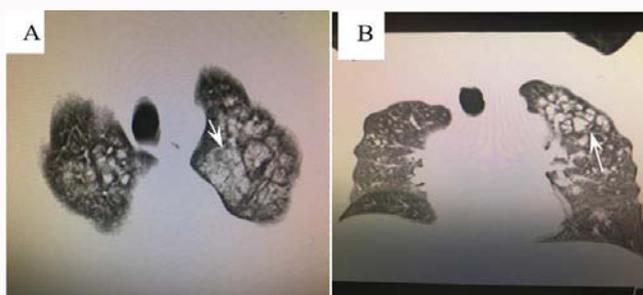
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**Figure 1:** Computed tomography of the lungs in 2016. Axial (A) and coronal (B) computed tomography of lungs shows calcifications (arrow) in both upper lungs; amorphous and multilobulated calcified masses (arrows) around the right shoulder (C).



**Figure 2:** Calciphylaxis on the left heel before operation.



**Figure 3:** Computed tomography of the lungs before operation in 2018. Axial (A) and coronal (B) computed tomography in lungs window shows more calcifications in both upper lungs.



**Figure 4:** Computed tomography of thoracic and hip joint shows severe vascular calcification of the chest wall (A) and lower limb (B).

motion was normal and with no pain. Tender and necrotic indurated plaques with surrounding erythema were noted on his left heel (Figure 2).

Blood tests revealed: Calcium 2.27 (2.02-2.57) mg/dl, phosphorus of 2.53 (0.6-1.6) mg/dl, and iPTH levels up to 2580.5 pg/ml. Parathyroid scintigraphy was performed 15 min and 2 h after injection of Tc99m MIBI. The Tc-99 MIBI scintigraphy demonstrated a focus of intense uptake in the upper pole of the right lobe, lower and upper pole of left lobe on the early and late images. CT scans show multiple, centrilobular, calcified nodules through-out both lungs (Figure 3A, 3B). The nodules were predominant in the upper and mid lung zones which was worse than 2016. Severe vascular calcification of thoracic and lower limb (Figure 4), multilobulated calcified masses around the right shoulder joint were found at the same time (Figure 5). X-ray of the knee joint showed stripe shaped calcification of lower extremity vessels (Figure 6A, 6B).

Total parathyroidectomy was performed in October 2018. Five parathyroid glands were excised (Figure 7). The pathological results



**Figure 5:** Computed tomography of the lungs before operation in 2018. The metastatic calcifications around the right shoulder joint and right chest wall increased significantly, adjacent ribs and soft tissue were compressed.



**Figure 6:** X-ray of the both knees before and after parathyroidectomy at 6 months. Preoperative left knee joint (A) and right knee joint (B) around the soft tissue tubular, cord like high-density shadow; X-ray of left knee joint.

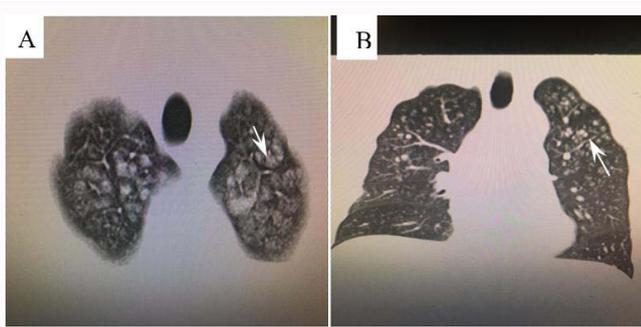


**Figure 7:** Five parathyroid glands were excised.

in adenomatoid hyperplasia. The pain of lumbosacral and lower limbs was significantly relieved the second day after operation, but the pain on heel ulcer was not relieved. The patient was re-checked 5 months after operation to evaluate the amelioration of metastatic calcification. CT scans revealed reduced metastatic pulmonary calcification (Figure 8A, 8B). Peri-articular soft-tissue calcifications of the right shoulder were barely visible (Figure 9). X-ray of knee joint showed have no change (Figure 10A, 10B). calciphylaxis on his left heel got worsen (Figure 11).

**Discussion**

With the advent of hemodialysis technology, the incidence of secondary hyperparathyroidism is rapidly increasing and metastatic calcification has become prominent. Metastatic calcification refers to the deposition of calcium in normal tissue, that is commonly



**Figure 8:** Follow-up computed tomography examinations. Axial (A) and coronal (B) computed tomography of lungs shows metastatic pulmonary calcification were remarkable absorption on image after five months operation in 2018.



**Figure 9:** Follow-up computed tomography examinations. soft-tissue calcifications of the right shoulder were barely visible.



**Figure 10:** X-ray of the both knees before and after parathyroidectomy at 6 months. (A) and right knee joint (B) at 6 months after operation showed no significant changes compared with those before operation.

associated with secondary hyperparathyroidism in patients on maintenance hemodialysis. Regions most commonly involved by this pathology are subcutaneous tissue, soft tissues of periarticular, vascular wall, internal organs [1]. In the presented case, a middle-aged patient suffered from multiple metastatic calcification due to secondary hyperparathyroidism. The biggest differences of our patient are the widespread metastatic calcification with pulmonary metastases, vascular calcification, soft tissue calcification surrounding large joint and calcific uremic arteriolopathy. To our knowledge, no similar researches have been reported in the past.

The diagnosis of secondary hyperparathyroidism is mainly depending on the history of chronic renal failure and elevated PTH levels, hypocalcemia and hyperphosphatemia were also observed.



**Figure 11:** The lesion progressed significantly after five months of parathyroidectomy.

Visceral calcinosis can affect lung, stomach, heart, pancreas, and kidneys, but lung is the most vulnerable organ [2]. The pathological characteristics of Metastatic Pulmonary Calcification (MPC) is calcium salt deposition in basement membranes of the epithelium and endothelium of pulmonary alveoli [3]. The main pathogenesis of MPC has not yet been illustrated, but some factors, such as hypercalcemia and hyperphosphatemia, dialysis-associated intermittent acid-base imbalance, and local secretion of free hydrogen ions in the lungs, kidneys, and stomach have been suggested as the risk factors for MPC formation [4]. The diagnostic rate of MPC is very low, but histological changes of MPC are seen at autopsy in 60% to 75% of maintenance hemodialysis patients [5]. This may probably due to insufficient sensitivity of chest X-ray examination, poorly understood about the imaging manifestations of MPC among clinicians, and the benign clinical course of the disease.

Chest radiographs are not very sensitive in the detection of MPC, especially in early stage of disease (small calcifications), and are usually show patchy or confluent airspace opacities or normal. CT has high sensitivity in an early detection of MPC. A chest CT scan of metastatic pulmonary calcification reveals of bilateral, diffuse, centrilobular, ground-glass nodular opacities and partially calcified nodules or consolidations, predominantly in the upper lung fields, is the most common finding on [5,6]. Calcium preferentially deposits in relatively alkaline tissues. The upper lung fields have high Ventilation/Perfusion (V/Q) ratio, creating high oxygen and low carbon dioxide levels.

The high V/Q ratio results in decreased PaCO<sub>2</sub> and increased pH [4]. Therefore, it had nothing strange that the lung apex is more commonly involved than the lung base. In our case showed symmetrical, multiple, centrilobular areas of ground-glass opacity throughout both upper lung area in 2016. Preoperative CT scan showed more calcareous were deposited in upper lung zones, but not in lung base, which was in accordance with the characteristics of MPC imaging changes. In addition, radionuclide imaging is another useful technique in finding out the early MPC, demonstrating generally symmetrical and increased radioactive isotope uptake in affected lung fields [7]. The pathological examination is the diagnostical golden standard for metastatic pulmonary calcification. However, it is largely limited in clinical applications since it is an invasive procedure.

MPC is a benign lesion, it generally slows progression in a long time, but it can also deteriorate rapidly within several weeks or months [8]. Most patients with MPC are asymptomatic, but several cases of hemoptysis, cough, dyspnea have been reported [2,9]. In our case, diffuse, patchy high-density shadows were found in both upper lungs

in 2016. The imaging changes of MPC were obviously aggravated in 2018 before operation, but throughout, the patient have no any respiratory symptoms. Preoperative pulmonary function test mainly shows mild restrictive ventilatory dysfunction. The pathological changes were absorbed gradually after five months of operation.

So far, the best treatment of MPC has not been established. The mainstay of treatment is normalization of phosphate and calcium levels, primarily with phosphate binders. Another means is too applicate of active vitamin D to control secondary hyperparathyroidism on the basis of maintaining normal calcium-phosphorus product [10]. Most of these patients with asymptomatic, non-progressive MPC do not need to intervention since these patients eventually died of other causes instead of MPC. Cases have been reported that MPC can be fully absorbed after parathyroidectomy [11,12]. More research's need to be done to see whether renal transplant is good for MPC [13]. In this case, the patient has no any respiratory symptoms, however, besides MPC, the patient had multiple periarticular metastatic calcifications, severe systemic vascular calcification, bone deformation, bone pain and calciphylaxis of the heel at the same time. Therefore, he underwent total parathyroidectomy. Five months after surgery a rapid regression of MCP was observed.

Soft tissue calcifications are another common manifestation of secondary hyperparathyroidism, characterized by large calcium phosphate deposition into cutaneous and subcutaneous tissues. Depositing of calcium salt in periarticular soft tissue region on patients of maintenance hemodialysis for chronic renal failure call Uremic Tumoral Calcinosis (UTC). Its estimated incidence is between 0.5% and 7% of hemodialysis patients [14]. It usually presents with benign nodules at periarticular sites, mainly manifests as firm, painless, lobular, tumor-like masses around the joints that can lead to limitation of movement of joint when large in size. The key feature is absence of erosion and destruction of nearby bone, and such lesions is reversible after medication or parathyroidectomy [15]. The sites commonly affected are soft tissues of periarticular shoulder, elbow, hip regions [16], other areas such as wrist [17], spine [18], and knee have been observed [19]. Our patient had extensive involvement of the shoulder and elbow; findings were consistent with metastatic calcinosis cutis secondary to TC. Why does it preferentially occur around joints? The exact mechanism behind this clinical entity is unknown. It may be related to the pH value of joint fluid, like the pathogenesis of gout. However, there have been no related experimental investigations published on this subject. In the natural course of such lesions is usually slow and progressive over several years [12]. Sometimes, too much tumoral masses leads to ulceration with superadded secondary infection. In this case, five months after surgery, a rapid complete absorption of the tumoral masses around the right shoulder and left were observed.

Additionally, this case also showed calcification in vessels along chest and limbs. There was no improvement in systemic vascular calcification, instead an aggravation of calcific uremic arteriolopathy on his left heel was observed. These results consistent with the previous reports [19,20], indicating that once calcification develops it probably cannot be reversed and tends to become more severe as time passes.

Overall, we report this case for the purpose of expanding the clinical and treatment of multiple metastatic calcifications in patient with SHPTH. MPC associated with uremia is potentially reversible, and can resolve after parathyroidectomy, but vascular calcification

cannot be reversed and tends to deteriorate as time passes.

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