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Case Report

Utility of Cinacalcet for Hypercalcemia and Parathyroid Hormone Suppression Secondary to Sarcoidosis in a Hemodialysis Patient

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Abstract

Introduction: Although sarcoidosis can affect any organ, end-stage renal disease (ESRD) is uncommon. Hypercalcemia may be a cause of renal failure. Hypercalcemia leads to worsening cardiovascular outcomes in hemodialysis (HD) patients. **Case presentation**: A 71-year-old Caucasian male presented with hypercalcemia and end-stage kidney disease as initial manifestations of sarcoidosis. The sole use of cinacalcet decreased serum calcium values and normalized parathyroid hormone (PTH). **Conclusions**: Cinacalcet, is a therapeutic opportunity to control hypercalcemia when traditional therapy is not effective or indicated. In dialysis patients with hypercalcemia, despite the absence of hyperparathyroidism, the use of calcimimetic drugs by controlling blood calcium levels can reduce vascular and cardiac valve calcifications which are the most frequent and most severe complications of CKD.

Keywords: Sarcoidosis, Hypercalcemia, Cinacalcet, Dialysis

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown cause; in Italy, it has an estimated prevalence of approximately 0.05% [1]. Sarcoidosis can affect all organs and tissues of the body, and its diagnosis can be difficult when pulmonary manifestations are lacking and the disease is paucysymptomatic or asymptomatic. Renal involvement is present in less than 5% of extrapulmonary cases [2]. Renal manifestations include hypercalcemia-hypercalciuria, tubulointerstitial nephritis, nephrocalcinosis and/or nephrolithiasis [3]. High levels of calcium, phosphate and parathyroid hormone (PTH) increase mortality in HD patients; thus, the US-based National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend maintaining the levels of calcium, phosphate and PTH in defined ranges (8.5-9.5 mg/dL, 3.5 -5.5 mg/dL, and 150-300 pg/mL) [4].

High levels of calcium and phosphate, in addition to dialysis treatment, increase mineral deposition in soft tissue, particularly arteries and cardiac valves, with an increased risk of fatal cardiovascular events [5].

Cinacalcet reduces calcium and phosphate levels in HD patients with secondary hyperparathyroidism (sHPT), improving survival and decreasing cardiovascular mortality [6].

Case presentation

A 71-year-old Caucasian male with end-stage renal disease was admitted to this unit to continue HD treatment. He also had a history of type 2 diabetes (for over 16 years), hypertension and benign prostatic hypertrophy. The patient had been in his usual health state until approximately 14 months before the current admission, when he experienced one week of diarrhoea, fatigue and decreased appetite that spontaneously resolved. Four weeks prior, the patient's blood creatinine level was 1.32 mg/dL, and three months later, his creatinine level was 2.32 mg/dL. Seven months after the episode of diarrhoea, fatigue and decreased appetite, he underwent tests to perform left knee prosthesis replacement surgery. Laboratory reports showed a creatinine level 8.9 mg/dL. He was admitted to the Nephrology Unit and diagnosed with end-

stage renal disease. At discharge, the preparation of a haemodialysis fistula was planned. Two months later, the patient was admitted to the Nephrology Unit of another hospital, and his laboratory reports confirmed a uremic state with glomerular filtration rate (GFR) of 6-7 mL/min, and hypercalcemia (2.77 mmol/L) as noted in previous examinations. Other laboratory findings were as follows: hemoglobin 11 g/dL, calcium 11.4 mg/dL, PTH 28 pg/mL and phosphorus 6.6 mg/dL. His vitamin D level was normal, with a low PTH level and unremarkable urinalysis.

An echocardiogram showed mild symmetric thickening of the left ventricular wall and normal biventricular function, and the size of the left atrial chamber was increased. There were calcifications in the mitral valve.

Chest computed tomography (CT) revealed bilateral hilar lymphadenopathy, and abdominal and renal ultrasound revealed a normal kidney size, regular contours, the preservation of parenchyma thickness, markedly echogenic renal parenchyma bilaterally, and atherosclerotic changes in the aorta.

A renal biopsy was performed and revealed twelve glomeruli on light microscopy (two sclerotic and ten normal) normal vessels, tubular atrophy and tubular obstruction by calcifications.

Immunofluorescence-labelling images were negative. A bone biopsy showed no increases in bone turnover or resorption by osteoclasts.

Milk-alkali syndrome was excluded, and the patient reported no intake of alkali, vitamin D, vitamin A or calcium supplements.

At that moment, all tests performed were negative, and all diagnoses were unconfirmed; however, therapy involved methyl-prednisolone (125 mg for three days) and bisphosphonates (pamidronate sodium 40 mg intravenously followed by alendronate 70 mg/week for oral use) and ultimately, after consultation with a rheumatologist, denosumab (60 mg, 1 subcutaneous vial) was started. The above mentioned therapies did not control the hypercalcemia, and the patient was discharged with the following diagnosis: "advanced renal insufficiency not classifiable as acute or chronic in hypercalcemia of a nature to be determined". Prednisolone was continued in tapering oral doses for two months without obtaining the reduction serum calcium. The steroid treatment resulted in severe worsening of glicemia control so it was discontinued.

Four months before the current admission, because of worsening renal disease, the patient was admitted to a third nephrology ward, and he initiated chronic HD (creatinine 9 mg/dL, GFR 5 mL/min, calcium 12.2-11.8 mg/dL, phosphorus 7.5 mg/dL, and PTH 12.5 pg/mL). After discharge, he underwent outpatient examinations non-invasive ultrasonography of the lower limbs showed severe peripheral obstructive arterial disease below the knees but in the absence of critical reduction in flows, while F-fluorodeoxyglucose (FDG) positron-emission tomography (PET) revealed marked FDG avidity in the mediastinal and hilar lymph nodes. Results from other laboratory tests are shown in Table 1.

At this point, the patient was admitted to our centre to continue HD treatment, and the examinations showed the following levels at admission: calcium 12.6 mg/dL (8.5 to 10.10 mg/dL), phosphorus 5 mg/dL (2.5 to 4.9 mg/dL) and PTH 6.5 pg/mL (15 to 88 pg/mL), 1,25-dihydroxyvitaminD3 45 pg/mL (19,2 to 67 pg/mL). The patient received on-line hemodiafiltration (HDF), the treatment was performed in post-dilution and against a 1.5 mmol/L calcium bath. We evaluated the available documentation related to eight months of testing and repeated a chest CT scan that confirmed the outcome of the previous examination. Endobronchial ultrasound - guided transbronchial needle aspiration (EBUS - TBNA) was scheduled, and then we continued the diagnostic process by performing thoracoscopy, with removal of a 4R lymph node and mediastinal fat. The histopathology report described non-caseating granulomas with giant cells compatible with the diagnosis of lymph node sarcoidosis and allowed us to exclude the presence of lymphoma. Lymphoma can be associated with sarcoidosis; in patients with this disease, there is a 5.5 to 11 time's higher incidence of lymphoma than in the rest of the population [7].

The pulmonologist advised against any therapy for stage I sarcoidosis (ESRD was caused by precipitation of calcium salts in the renal tubules secondary to hypercalcemia; no non-caseating granulomas were present on renal biopsy). However, it was necessary to effectively control the hypercalcemia, which was causing serious damage to the patient, particularly when considering cardiovascular complications due to the comorbidities present (i.e., diabetes and kidney failure).

The use of corticosteroids previously attempted elsewhere had not yielded good results and worsened the control of glucose metabolism why the patient did not want to try steroid treatment again; therefore, in agreement with the patient, we started cinacalcet (off label; 30 mg in the evening increased to a dose of 60 mg with excellent results), obtaining progressive reduction and normalization of calcium levels over the subsequent 18 months (until the patient was transferred to another location), in the absence of noteworthy side effects and with a parallel modest increase in PTH values up to 16.8 pg/mL (15 to 88 pg/mL). After three months from the beginning of the therapy the patient consulted an endocrinologist who advised against the use of cinacalcet so at the next dosages the serum calcium was again high and the patient resumed taking the drug.

During our observation the 1,25-dihydroxyvitaminD3 values remained within the normal limits with variations from 38 to 55 pg / mL (19,2 to 67 pg/mL), albumin levels ranged from 3.7 to 2.6 g /

dL (3,5 to 5,2 g/dL) and high C-reactive protein values from 3 to 5,4 mg/dL (< 0,30 mg/dL) were related with cardiovascular events.

Normal values of 1,25-dihydroxyvitaminD3 are unusual for patients with severe reduction in renal function and in patients on chronic dialysis as serum dosages decrease in proportion to the loss of renal function [8].

Normal vitamin D values explained the concomitant hypercalcemia of our patient while the stable levels of vitamin D over time was compatible with the stationarity of the pathology detected at follow-up.

Chest CT scan, performed after 1-year e and after 18 months, was negative for presence of pulmonary infiltrations and confirmed the stability of the findings previously found. Lymph node calcifications, a sign of chronic disease [9, 10], were absent. The patient did not show signs and symptoms of sarcoidosis involvement of other organs and / or tissues or of progression of the disease.

Subsequent significant events that occurred during the patient's stay in our ward were progression of peripheral artery disease with angioplasty of the lower left limb and an episode of acute coronary syndrome followed by coronary angiography and percutaneous coronary intervention.

Discussion

Sarcoidosis is a self-remitting disease with remission or resolution within 1-3 years, and most patients do not require any treatment. Approximately one-third of patients evolve in a chronic course requiring prolonged use of medications. Corticosteroids are the first-line treatment, and very few patients do not respond or show unacceptable side effects [11].

We did not repeat the use of corticosteroids, even at different dosages or with different molecules, as we did not want to complicate the difficult control of glucose metabolism to the patient, who was already being treated with insulin and refused steroid treatment. Glucocorticoids usually cause a reduction in total calcium within a few days, followed by a fall in urinary calcium losses within 7-10 days [12]. In the absence of a response within 2 weeks, it is necessary to evaluate other diagnostic hypotheses such as primary hyperparathyroidism, neoplasms, lymphoma and multiple myeloma [12]. In our case, corticosteroid treatment had been extended beyond 2 weeks and all alternative diagnostic hypotheses already discarded.

The choice to treat a patient with sarcoidosis requires a risk/benefit balance considering several factors, and not all patients must necessarily be treated or treated equally [13].

Given the limitation of sarcoidosis to the mediastinal lymph nodes and good prognosis with spontaneous resolution of the disease in more than half of patients in stages I and II of the disease [14], we considered it excessive to expose the patient to immunosuppressive therapies as II, III and IV choices [11].

Amino bisphosphonates and denosumab, drugs whose action aims at reducing bone remodelling, had been prescribed in other centers, regardless of whether bone biopsy revealed any signs of high bone turnover or osteoclastic hyperactivity, proving to be ineffective.

Regarding the strategy to reduce serum calcium, we evaluated the effects of activated vitamin D and the expression and function of calcium-sensing receptor (CaSR) to find a possible therapeutic solution.

Excluding bone as a source of calcium release (bone biopsy) and renal reabsorption (GFR <5 ml/min), the cause of elevated blood calcium values remained intestinal absorption mediated by high or normal vitamin D values [15, 16] and the calcium gain from dialysate.

Concentrations of 1.25 mmol / L of calcium in the dialysis bath allow a greater mass transport of calcium compared to higher concentrations (1.5 and 1.75 mmol / L) other factors being equal (ionized calcium concentration gradient between blood and dialysate, ultrafiltration volume and treatment time) [17], when pre-dialysis serum calcium is high, single treatment losses are greater. In HDF in post- dilution, with the same difference in calcium concentration between blood and dialysate, the calcium balance is similar to HD [18]. In patients with suppressed PTH and signs of low bone turnover, the reduction of serum calcium with the use of low calcium concentrates results in an increase in PTH to more adequate levels and an improvement in the indices of low bone turnover [19, 20].We chose to use the dialysis bath concentration of 1.5 mmol / L to minimize the effect of the dialysis treatment on mineral metabolism. The high levels of ionized calcium (1.38-1.28 mmmol / L, normal value 1.13-1.32 mmol / L) still allowed adequate calcium losses at each session (Table 2) under condictions of hypercalcemia.

Cinacalcet presented itself as a possible candidate to solve the patient's problems given its mechanism of action on the CaSR, which is located not only in the parathyroid glands but also in other target organs such as the kidneys and intestines [21].

Activation of CaSR by agonists leads to phospholipase C G-protein-mediated activation, activation of the inositol triphosphate cascade, intracellular calcium mobilization, the activation of protein-kinase C (PKC) and the inhibition of adenylyl-cyclase [22]. The cellular effects are different depending on the target organ involved. At the level of the parathyroid glands, the activation of CaSR determines a reduction in PTH secretion; at the renal level, there is a decrease in the tubular reabsorption of calcium and in the intestine, it inhibits the intestinal absorption of calcium [22].

Cinacalcet is an allosteric modulator of CaSR that increases the sensitivity to extracellular calcium and reduces the concentration of calcium in all target organs [23].

In our case, using cinacalcet, we could expect the following results: no effect on PTH since the patient already had a suppression of secretion, no effect on the kidney given the advanced degree of renal insufficiency, and a reduction in intestinal absorption, which we hoped was sufficient to translate into a significant reduction in serum calcium. We started the treatment with confidence, as the drug was well known and routinely used in our department for the treatment of sHPT in dialysis patients, as indicated in the technical data sheet. We started with 30 mg/day and peaked at 60 mg/day (Table 3). The results obtained showed how the inhibition of intestinal calcium absorption was adequate to reduce serum calcium from the first month of administration, with fluctuations in serum calcium due to the patient's difficult pharmacological compliance, as demonstrated by the non-optimal control of serum phosphorus levels (Table 3). Recall that the patient had stopped the drug for over a month on the advice of a specialist.

After 4 months of therapy, the PTH value showed a weak but progressive increase (Figure 1) despite the maintenance of calcium mimetic therapy, suggesting that the modulation exerted by cinacalcet on the CaSR of the parathyroid glands, under conditions of prolonged normal serum calcium levels, was adequate to favour the secretory stimulus for PTH.

The increase in PTH values cannot be attributed to the normalization of serum calcium values alone, as the hypocalcemic therapy in place involved the exclusive use of cinacalcet which has a powerful action in reducing PTH secretion both in the presence of high total calcium levels than in the presence of hypocalcemia or eucalcemia as found in primary hyperparathyroidism (pHPT) and sHPT respectively [24].

The available studies on the properties of CaSR show a complex functioning capable of activating different protein kinases (PKs) which can also negatively modulate the activity of CaSR [25].

The role of various PKs in controlling CaSR-mediated PTH secretion is not yet clear [26] and it is difficult to understand the increase in PTH that occurred in our patient during therapy with calcimimetics.

We can attribute the eucalcemic state and the increase in PTH secretion to the use of cinacalcet, as these effects began and persisted after the suspension of cortisone, bisphosphonates and denosumab (Table 2).

The limited observation period following transfer to another dialysis centre did not allow us to better document the effect on PTH. Furthermore, we could not use etelcalcetide (given intravenously) because it was not yet available in our center. The use of this product would have made it possible to overcome the patient's compliance problems.

The increasing trend of PTH values obtained with calcium mimetic therapy promised to protect the patient from the condition of low bone turnover due to prolonged hypercalcemia. The patient also had other clinical conditions commonly associated with low bone formation such as diabetes, aging, malnutrition and inflammation [27, 28] it was therefore important to maintain normal bone formation by removing PTH suppression and bringing PTH values closer to KDOQI indications.

Our goal was to maintain serum calcium in the normal or near-normal range; cinacalcet was well tolerated and met expectations.

Given the success achieved, maintenance of eucalcemia with cinacalcet should has been continue, at adequate doses, until normalization of the calcium obtained by remission of the disease or by the introduction of immunosuppressive therapy following clinical progression.

The results obtained in this patient suggest that a timely diagnosis and an early and prolonged treatment of hypercalcemia with calcimimetics could positively modify the cardiovascular outcome of the dialysis patient even in the absence of secondary hyperparathyroidism.

An obtained and unexpected result was the progressive increase of PTH values during cinacalcet therapy. This finding is very interesting, as relatively high PTH values are considered necessary to maintain adequate turnover and mass bone in-patient on dialysis.

Cinacalcet is approved for pHPT, sHPT and parathyroid carcinoma-associated hypercalcemia, the use of cinacalcet has been described to control malignancy-associated hypercalcemia [29]. Calcimimetics and cinacalcet paricularly are not included among the treatments of sarcoidosis. To the best of our knowledge, the use of cinacalcet in sarcoidosis-associated hypercalcemia has not been reported earlier. We also have no news of its use in dialysis patients with suppressed PTH.

Negative laboratory test	Negative diagnostic test
Alkaline phosphate	Chest X-ray
Prostate-specific antigen	Skeletal X-ray
Tumour markers	Radionuclide bone scan
Serum protein electrophoresis	Upper and lower endoscopy
Serum protein IFE	Thyroid and parathyroid ultrasound
Bence-Jones proteinuria	Bone marrow biopsy

Table 1: Laboratory and diagnostic tests with negative results.

Date	Predialysis serum calcium (8,5-10,1 mg/dL)	Postdialysis serum calcium (8,5-10,1 mg/dL)	Albumin (3,5-5,2 g/dL)	1-25 dihydroxyvitamin D_3 (19,2-67 pg/mL)
arrival at the ward	12,6	10,6	3,3	42
month 1	12,4	10,4	3,2	
month 2	11	10,5	3,3	45
month 3	10,7	10,3		
month 4	11,1	10,7		
month 5	9,5	9,6		38
month 6	10,7	9,8		
month 7	9,7	10		
month 8	12,3	10,7	3,3	50
month 9	12,8	10,8	3,7	
month 10	11,9	10,9		
month 11	9,2	9,4		47
month 12	7,7	9,2	2,16	
month 13	8,6	9,4		
month 14	9	9,3		55
month 15	9,1	9,5	2,69	
month 16	9,7	9,7		
month 17	11,1	10,1		44
month 18	10,5	10	2,7	

Table 2: Levels of serum calcium pre/post HDF, albumin and 1-25 dihydroxyvitamin D_3. Each treatment was performed using a 1.5-mmol / L calcium bath. Cinacalcet was started 40 days after patient arrival. The values for months 8 and 9 refer to the voluntary suspension of cinacalcet carried out by the patient.

Date	Calcium mg/dl	Phosphorus mg/dl	Calcium x Phosphorus	PTH pg/ml	Sevelamer carbonate	Sucroferric hydroxide	Pamidronate/ Alendronate	Denosumab	Cinacalcet
- month 7	11.4	6.6	75.24	28	800 mg x3/ day				
- month 6							Pamidronate 40 mg 1 f	Prolia 60 mg 1 f	
- month 4	11.8	7.5	88.5	12.5			Alendronate 70 mg/ sett.		
Month of arrival at the ward	12.6	5	63	6.5	800 mg x3/ day	500 mg x3/ day			
+ month 1	10.7	6.5	69.55		800 mg x3/ day	500 mg x3/ day			30 mg/ day from 07/12/16
+ month 2	9.5	5.6	53.2	8.8	800 mg 2 cp x3/day	500 mg x3/ day			30 mg every other day with 60 mg
+ month 3	9.7	6	58.2		800 mg 2 cp x3/day	500 mg x3/ day			30 every other day with 60 mg
+ month 4	12.8	6.3	80.64		800 mg 2 cp x3/day	500 mg x3/ day			60 mg/day
+ month 5	9.2	2.6	23.92		800 mg 2 cp x3/day	500 mg x3/ day			60 mg/day
+ month 6	7.7	6.1	46.97	13.5	800 mg 2 cp x3/day	500 mg x3/ day			60 mg/day
+ month 7	8.6	6.3	54.18		800 mg 2 cp x3/day	500 mg x3/ day			60 mg/day
+ month 8	9	5.2	46.8		800 mg 2 cp x3/day	500 mg x3/ day			30 mg every other day with 60 mg
+ mese 9	9.1	4.8	43.68	16.8	800 mg 2 cp x3/day	500 mg x3/ day			30 mg every other day with 60 mg

+ month 10	11.10	6.5	72.15		800 mg 2 cp x3/day	500 mg x3/ day			30 mg every other day with 60 mg
+ month 11	10.5	5.2	54.6		800 mg 2 cp x3/day	500 mg x3/ day			30 mg every other day with 60 mg

Table 3: Levels of calcium, phosphorus and PTH with reference to the execution times of the tests and therapies.

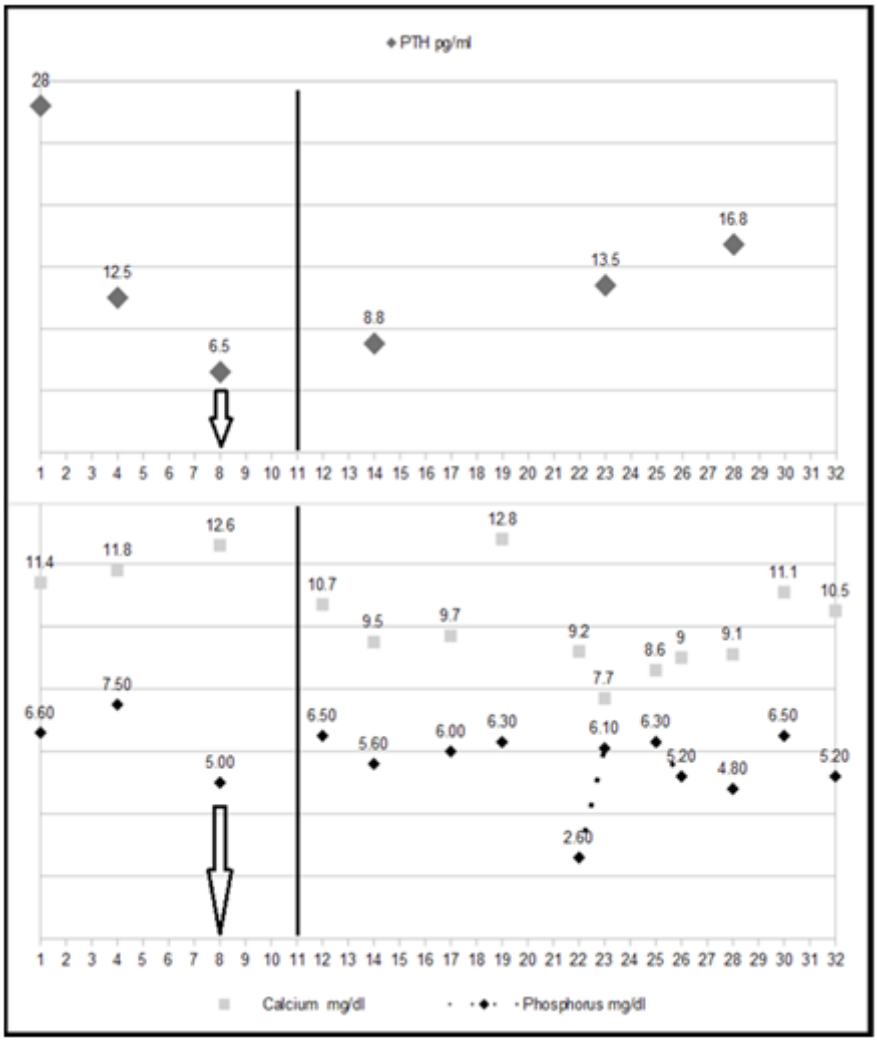

Figure 1: Trend in calcium, phosphorus and PTH levels with particular reference to the time of arrival of the patient at our centre (arrows) and the beginning of calcium mimetic therapy (black vertical line). **Note**: (In the right and top part of the figure) the progressive increase in the PTH values following the containment of calcium values (right wall at the bottom of the figure).

Conclusion

In spite of the good prognosis of sarcoidosis, an early diagnosis is necessary, especially when hypercalcemia and hypercalciuria are present to prevent worsening renal function even in the absence of renal involvement of the disease.

In patients with chronic renal failure, the correction of hypercalcemia is essential to limit cardiovascular involvement.

In the control of hypercalcemia secondary to sarcoidosis, cinacalcet can be an interesting drug to use in the early stages of the disease to prevent kidney damage in subjects who do not respond to corticosteroids or traditional therapies and in diabetic patients to avoid complications related to the use of corticosteroids.

In dialysis patients with sarcoidosis and hypercalcemia, for all the absence of sHPT, calcium mimetics could improve morbidity and survival by correcting calcium and PTH alterations. Studies dedicated to patients with suppressed PTH could be useful to better understand the multiple functions of the calcimimetic drugs.

Availability of Data and Materials

Data and materials were extracted from patient medical records.

Ethics and Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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